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Original Communications

THE PRODUCTION OF A PRESSOR SUBSTANCE BY THE TOTALLY ISCHEMIC KIDNEY

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IN 1934, Goldblatt, Lynch, Hanzal, and Summerville demonstrated that partial renal ischemia produces permanent hypertension. Houssay and Fasciolo, in 1937, proved that the ischemic kidney produces a pressor substance. When an ischemic kidney is grafted into the neck of a recently nephrectomized dog, a rapid elevation of blood pressure results; this does not occur after grafting a normal kidney. In 1938, Houssay and Taquini showed that plasma from the renal vein of the ischemic kidney, *in situ*, has a marked vasoconstrictor action on the Läwen-Trendelenburg preparation of the toad and of the posterior extremities of the dog, whereas venous blood from a normal kidney lacks this action.

Volhard and his associates (Hartwich and Hessel, 1932) attempted to show that impairment of the renal circulation produces a pressor substance. For this purpose, they studied the changes in arterial pressure several hours after total ligation of the renal artery. Likewise, in 1937, Goldblatt found, after completely occluding both renal arteries, that severe uremia resulted, with only slight elevation of arterial pressure. Dicker (1937) tied both renal pedicles of dogs for twenty-four hours, and then observed, on removing the ligatures, a definite rise in arterial pressure.

One may object to these experiments on the ground that total renal ischemia causes necrosis of tissue; they are, therefore, less physiologic than those producing partial ischemia, in which the living kidney produces a pressor substance for months or years. We have thought it useful, however, to investigate this total renal ischemia for several reasons: (1) to see whether the totally ischemic kidney produces vasoconstrictive substances—as Volhard affirms but many dispute; (2) to learn whether the pressor substances from totally and partially ischemic kidneys are similar; (3) to employ a technique which should permit one

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to obtain the pressor substance more easily, quickly, and safely, facilitating chemical and pharmacologic study.

EXPERIMENTAL STUDY

Experiments have been done to learn (1) whether the totally ischemic kidney can produce arterial hypertension, (2) whether the totally ischemic kidney produces a pressor substance, and, (3) if there is such a substance, the mechanism of its action.

To study the first point we have produced total renal ischemia in ten dogs by the following technique: (1) in three dogs both renal pedicles were clamped completely; (2) in four dogs, only the renal arteries were occluded; (3) in three, both pedicles were clamped (as in the first group), but they were also tied with strong ligatures, so that, even when the clamps were removed, the circulation was interrupted. Chloralose anesthesia was used in all of the operations. In some, the anterior operative approach was used, in others, the lumbar. The clamps were so placed that the incision could be closed almost completely and yet they could be removed from the outside with a minimum of trauma. The occlusion was maintained under anesthesia for five and one-half to six and one-half hours. After the clamps were removed, the changes in the femoral arterial pressure were registered. In group one there was

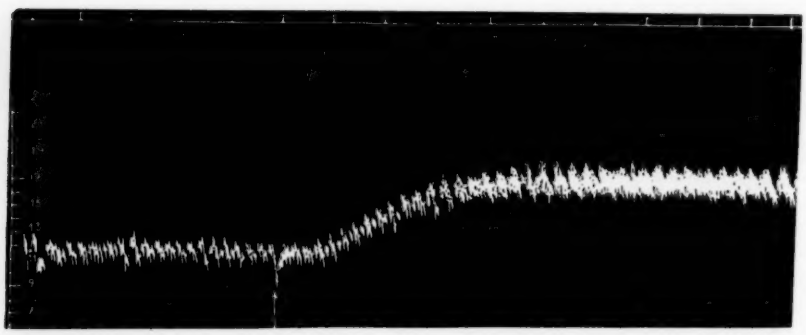

Fig. 1.—Changes in blood pressure after restoration of blood flow through totally ischemic kidney. Arrow indicates time of removing clamps from renal pedicles (chloralosed dog).

an immediate rise in blood pressure on releasing the clamps, amounting to 20, 30, and 65 mm. Hg, respectively, and this continued throughout the experiments (Fig. 1). Later examination of the pedicles showed that the circulation had been completely restored. In group two, in which only the arteries were occluded, there was in two dogs a definite rise in blood pressure, amounting to 55 and 60 mm. Hg, respectively, but in the other two there was no change. Later examination showed that in the first two the circulation had been restored completely, whereas in the last two there was complete thrombosis of the renal artery. In group three, in which both clamps and ligatures were used, removing the clamps alone produced no change in blood pressure.

We see, therefore, that in the five dogs in which the renal circulation was re-established after total ischemia lasting five and one-half to six and one-half hours, an increase in arterial pressure resulted. In the five dogs, however, which underwent the same operation, but whose renal circulation was not re-established, the arterial pressure remained unchanged (Fig. 2).

From these experiments one can conclude (1) that the increase in pressure is not the result of a reflex secondary to removal of the clamps, and (2) that when the circulation of the totally ischemic kidney is re-established, a rise in arterial pressure occurs.

Having shown that the totally ischemic kidney can produce hypertension, we were interested in learning how it does so. For this purpose we employed the method of grafting used by Houssay and Fasciolo in experiments with partially ischemic kidneys. Sixteen totally ischemic kidneys were grafted into the necks of sixteen normal dogs. According to the technique and results, we have classified the experiments into three groups: A, B, and C.

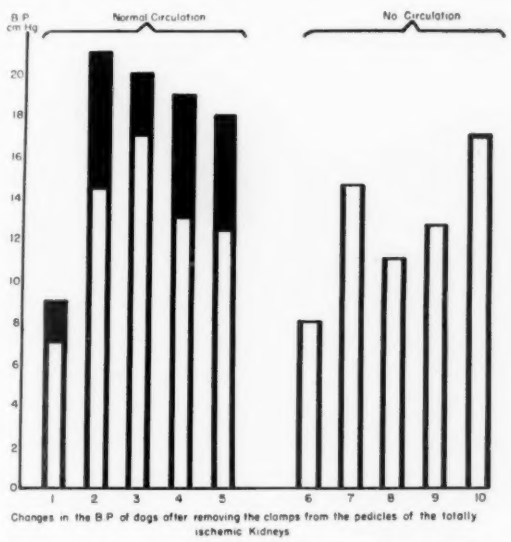

Fig. 2.—Changes in blood pressure after removing clamps from the renal pedicle of the ischemic kidney. Each column represents one experiment. White—blood pressure before removing clamps; black—change following removal.

In group A, first, under cloralose anesthesia, the left renal artery was clamped through the abdominal incision, and the collateral circulation of that kidney then cut off by removing the perirenal fat. After five to seven hours the kidney was removed and promptly grafted to the neck of a normal dog whose renal pedicles had been tied off. With this technique, ten totally ischemic kidneys were grafted into ten dogs, in nine of which there was a rise of arterial pressure, amounting to 30, 40, 40, 45, 50, 50, 55, 70, and 75 mm. Hg, respectively (Fig. 3). In one dog the increase was negligible, namely 7 mm. Hg.

In group B, consisting of four dogs, the renal artery was occluded by the lumbar route, extraperitoneally, without disturbing the perirenal fat. Six or seven hours later these kidneys were grafted to the necks of normal dogs whose renal pedicles had been occluded, and no change in blood pressure was observed.

Finally, group C comprised experiments on two dogs with two renal arteries to each kidney. In both, one of the two arteries was occluded and the collateral circulation destroyed. Seven hours later the kidney was grafted by means of the occluded artery, and no change in the blood pressure of the dog was observed.

In summary, the results in these three groups of experiments were as follows: (1) in ten experiments, when the ischemia was complete, there was a definite rise of blood pressure in nine of the recipient dogs; (2) in the other six experiments, in which the ischemia was not complete, in four because of the remaining collateral circulation, in two because only one of the two renal arteries supplying each kidney was occluded, grafting produced no change in blood pressure (Fig. 4).

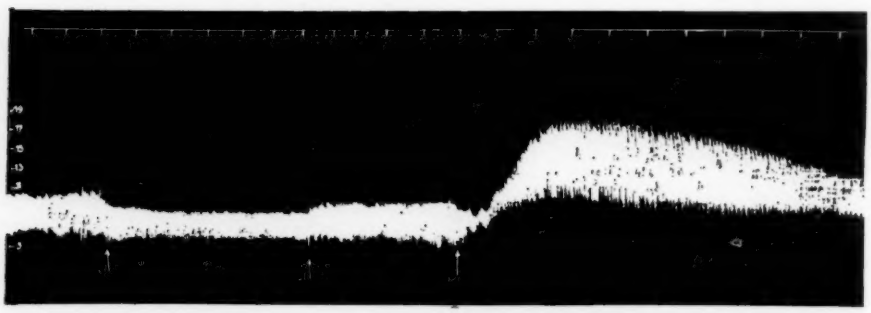

Fig. 3.—Changes in blood pressure following grafting of a normal and a totally ischemic kidney into the neck of a normal dog. First arrow—time of grafting normal kidney; second arrow—time of removal of this kidney; third arrow—time of grafting totally ischemic kidney.

The fact that the totally ischemic kidney liberates a pressor substance into the blood has been confirmed by direct injection of blood from the renal vein. One kidney pedicle of the dog was clamped for six hours, after which blood was collected from this and from the other kidney vein. One hundred cubic centimeters of blood from the kidney whose pedicle had been clamped was injected. The normal blood produced no change in blood pressure, whereas the blood from the totally ischemic kidney caused a definite rise (Fig. 5) (Houssay, Braun-Menendez, Fasciolo, and Taquini, unpublished data). Therefore, we can affirm that acute, complete ischemia of the kidney produces a pressor substance, as the partially ischemic kidney does.

Since total renal ischemia produces an elevation of blood pressure as a result of the liberation of a pressor substance, it remained to determine the mechanism of action of this substance. Therefore, the vasoconstrictive action of the plasma of the blood from the totally ischemic kidney was compared with that of the totally ischemic spleen, and that

of the remaining normal kidney of each dog used in the previous experiments. In each experiment, when the blood from the kidney was obtained, especial care was taken to exclude blood from the suprarenal glands. The pressor power of the plasma of every sample of blood was studied by direct perfusion through the vascular system of the toad. The method of Läwen-Trendelenburg was used, and the technique was the same as that employed in our experiments with partially ischemic kidneys.

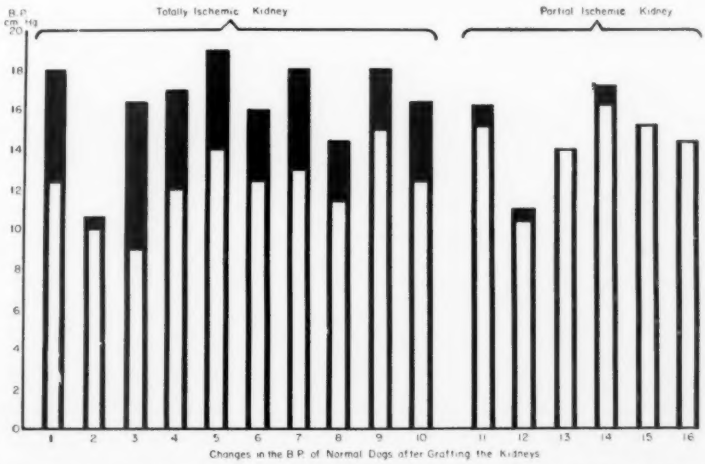

Fig. 4.—Changes in blood pressure resulting from the grafting of a totally ischemic and a partially ischemic kidney. Each column represents one experiment. White—blood pressure before grafting; black—blood pressure following grafting.

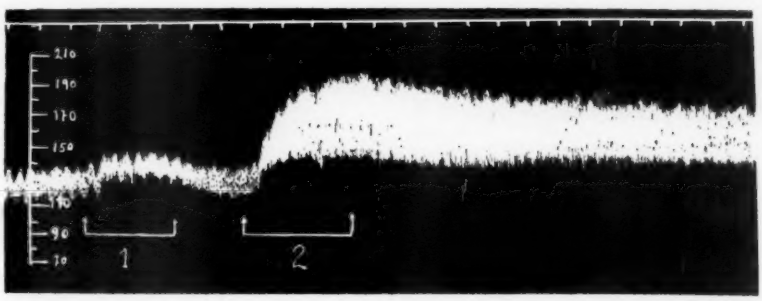

Fig. 5.—Changes in blood pressure of a normal dog following: *1*, Injection of 100 c.c. of venous blood from normal kidney; *2*, injection of 100 c.c. of venous blood from totally ischemic kidney.

The results showed that in all of the experiments in which the graft produced a rise in blood pressure in the recipient dog the plasma had a marked vasoconstrictive power, but in those in which the incompletely ischemic kidney had not changed the blood pressure of the recipient dog the corresponding plasma showed little or no vasoconstrictive power. The plasma of effluent blood from the normal kidney and the totally ischemic spleen possessed no vasoconstrictive power (Table I). The pressor action of the plasma of effluent blood from the totally ischemic kidney was tested also on the vascular system of the legs of dogs, according to the Sollmann technique, with the same results.

We can conclude, therefore, that the substance liberated by kidneys which have been rendered acutely and totally ischemic acts, like that produced by the partially ischemic kidney, directly upon the peripheral vascular system, causing vasoconstriction and hypertension.

TABLE I

EXP.	DURATION OF TOTAL ISCHEMIA	RATE OF PERFUSION IN THE PREPARATION OF LÄWEN-TRENDELENBURG DROPS PER MINUTE				ARTERIAL PRESSURE OF THE NORMAL DOG AFTER GRAFTING THE ISCHEMIC KIDNEYS		
		RINGER'S SOLUTION	PL. FROM RENAL VEIN OF NORMAL KIDNEY	PL. FROM THE TOTALLY ISCHEMIC KIDNEY	PL. FROM THE SPLENIC VEIN	INITIAL B.P. OF THE DOG	FINAL B.P. OF THE DOG	VARIATION IN CM. HG
1	6 hours	60	66	14	–	12½	18	5½
2	6½ hours	71	75	2	70	9	16½	7½
3	6 hours	56	63	7	60	12	17	5
4	7 hours	61	44	3	59	14	19	5
5	6 hours	82	86	37	86	12½	16	3½
6	7 hours	70	66	8	–	11	18	7
7	6 hours	56	58	12	–	11½	14½	3
8	6 hours	58	50	5	–	15	19	4
9	7 hours	58	59	12	–	12½	16½	4
10	5 hours	65	68	64	72	10	10.7	0.7
11	6 hours	58	43	43	–	15½	16¼	0.75
12	6 hours	57	63	54	–	10½	11	0.5
13	7 hours	70	72	68	–	14	14	–
14	7 hours	62	60	60	–	16½	17¼	0.75
15	7 hours	64	60	64	–	15	15	–
16	7 hours	72	74	70	–	14½	14½	–

CONCLUSION

1. The re-establishment of the circulation to a previously totally ischemic kidney causes a rise in the arterial pressure.

2. This rise is caused by the liberation of a pressor substance formed during the total renal ischemia.

3. This substance acts directly upon the peripheral vessels and produces marked vasoconstriction and consequent hypertension.

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TWO UNUSUAL TYPES OF ELECTROCARDIOGRAMS*

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CONSIDERABLE information concerning the physiologic properties of the heart is often obtained from its unusual and rare behavior, and this applies to unusual electrocardiograms. It is as much for this reason as to put on record two apparently hitherto unreported electrocardiographic abnormalities that the following communication is made.

CASE I. INTERPOLATED, BLOCKED-OUT, AURICULAR PREMATURE SYSTOLES

This patient was a 63-year-old man who had a series of records taken in order to discover the nature of an arrhythmia clinically diagnosed as paroxysmal auricular fibrillation. The first (Fig. 1) was abnormal, and showed sinus arrhythmia. The third (Fig. 4) showed short runs of paroxysmal auricular fibrillation. The second, reproduced in Fig. 2, revealed a peculiar, hitherto undescribed arrhythmia. Analysis of the record disclosed the fact that every ventricular beat was followed by an auricular premature systole, which was conducted to the ventricle only once; the others were blocked out. Examination of Leads I and II, by themselves, gives the impression superficially of sinus bradycardia, with what seems to be a premature systole of auricular origin in Lead I. The true nature of the arrhythmia is revealed, however, in Leads III, CF_2 (4), and CF_4 (5). Lead CF_2 is the one which disclosed the true mechanism best, and it is reproduced in Fig. 3, with measurements between the various deflections.

This record of Lead CF_2 shows sinus rhythm, at a basic rate of 92 per minute, which is disturbed by auricular premature systoles. These premature systoles follow every ventricular beat, and all but one are blocked out. The exception is X_7, which is an ordinary, conducted, auricular premature systole. Of the remaining, blocked-out, premature auricular systoles, six (X_2, X_3, X_4, X_5, X_9, and X_{10}) are followed by a pause before the sinus beat is resumed, and the interval is 1.25 seconds.† In the case of X_1, X_6, and X_{11}, however, there is no such pause; the sinus beat occurs 0.64 to 0.65 sec. after the previous sinus beat. Since the interval between sinus P waves in these shorter cycles is approximately one-half that of the longer sinus cycles, viz., 0.65 sec., it is apparent that the shorter cycles represent the true sinus rate, and that in these cycles the premature systoles are interpolated. In Lead III there are two, and, in Lead CF_4, four, such interpolated, blocked-out, auricular premature systoles. Measurements of the cycle lengths in Lead I show

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†These intervals are indicated in hundredths of a second above the record with the decimal point omitted.

that the apparently premature complex in this lead is another sinus beat which is preceded by an interpolated, blocked-out, premature systole.

The possibility was considered that the premature systoles were of a parasystolic nature, with a rate equal to the sinus rate. Against this is the fact that the P-wave contour of these premature systoles varies, and, what is more important, that the *X-X* interval (the interval between premature systoles) is not constant. In most instances it is 0.64 to 0.66 sec., or 1.24 to 1.26 sec., but X_7-X_8 is 0.52 sec., and X_8-X_9 is 0.74 sec. It is difficult to see how such a variation in the cycle length could occur if the mechanism were parasystole.

Fig. 1.

The measurements support the view that the mechanism is caused by a re-entry phenomenon, for fixed coupling is present. The re-entry is not located in the ventricles, because the *R-X* interval (the interval between the onset of the preceding QRS and the onset of the premature auricular complex) in one instance (R_8-X_8) is out of line with the rest. It is 0.30 sec., whereas all other *R-X* intervals are 0.34 to 0.36 sec.

The location of the re-entry is apparently supraventricular, for the premature systole follows the preceding P wave at a fixed interval in every case, even after the conducted premature systole (X_7). Thus X_7-X_8 is 0.52 sec., as compared with the P-X intervals of 0.48 to 0.50 sec. There is evidence that the re-entry is mediated within the A-V node. This is based on the fact that the only premature systole which is followed by a second is X_7, and this is the only premature beat which is conducted to the ventricle. There is no reason to assume that the auricle was not responsive 0.50 sec. after the other premature systoles, for the interpolated premature systoles evoke a response in the form of a sinus P wave after an interval of only 0.15 sec. Nor can interference account for the failure of the nonconducted premature systoles

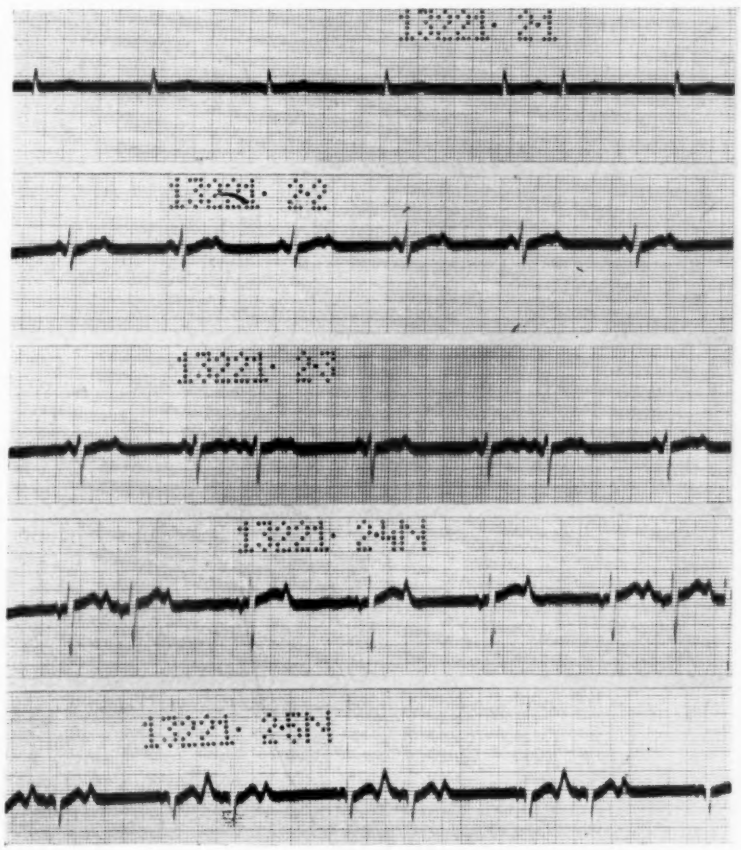

Fig. 2.

to re-enter, because the record shows that there could be no interference 0.50 sec. after the noninterpolated premature systoles. It would thus appear that re-entry could not occur unless the impulse of the auricular beat, whether from the sinus or premature, entered the A-V node on its way to the ventricle. Only when this occurred was the bypath reached

along which re-entry to the auricle could take place. Transmission to the ventricle was prevented in all but the one instance because of the longer refractory period of the A-V junctional tissue below the point of re-entry.

Ordinarily, the pause after an auricular premature systole is equal to, or slightly longer than, the cycle length of the sinus beats, and the interval between the sinus P before, and that after, the premature systole is less than two sinus cycles. This occurs because the premature systole reaches the sinus node prematurely, and discharges it ahead of time. Under rare circumstances, when the premature auricular systole fails to reach the sinus node prematurely, the sinus rhythm is not affected, and the interval between the sinus P before, and that after, the premature systole equals two sinus cycles. In the case reported here, the *P-P* interval of the sinus beats between which premature systoles were interpolated was 0.65 sec. The longer sinus intervals were 1.25 sec., which is 0.05 sec. less than twice the shorter sinus P intervals. It would appear, therefore, that the auricular premature systoles, in most instances, did reach the sinus node and discharge it prematurely. The fact that the *X-P* interval was 0.10 sec. longer than the *P-P* interval (0.75, less 0.65) shows that it took 0.10 sec. for the impulse from the ectopic pacemaker to reach the sinus node, and the sinus node was discharged just 0.05 sec. before it would have done so spontaneously (*P-P* interval, less sum of *X-P* interval, plus conduction time from ectopic focus to sinus node $= 0.65 - [0.50 + 0.10]$).

Therefore, the fact that some of the premature systoles were interpolated must have been the result either (1) of a slight delay in the time of arrival of the ectopic impulse at the sinus node, sufficient to permit the latter to discharge at its usual time, or (2) of the development temporarily of unidirectional block localized to the region around the sinus pacemaker, the so-called "protection block," which prevented the ectopic beat from reaching the sinus node. In either case there must have been, in addition, a rather short duration of the refractory period of the auricles, which permitted them to begin to respond within 0.15 sec. after the onset of the previous auricular impulse. This hyperirritable state of the auricle was probably responsible for the short paroxysms of auricular fibrillation which are seen in the next tracing (Fig. 4).

The alternate possibility that the sinus node was not discharged prematurely by the ectopic impulse, but was constantly protected by an "entrance block," cannot be excluded, but the evidence outlined above appears to be against it. If the presence of a continuous protection block is assumed, then a variable "exit" block must also be assumed to account for the longer sinus intervals.

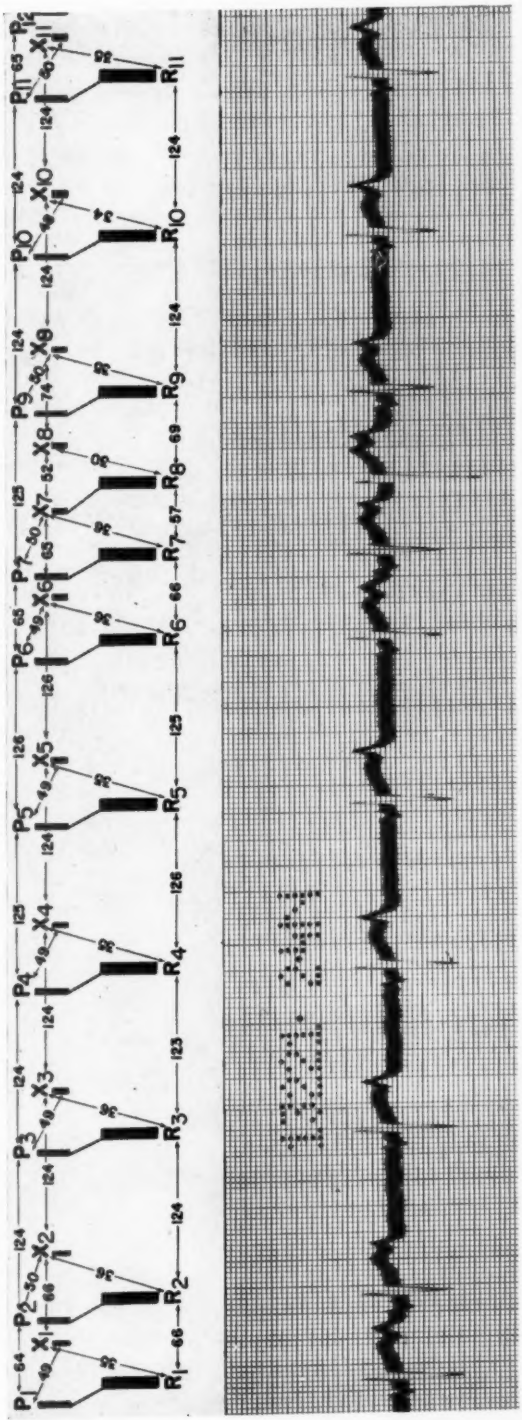

Fig. 3.

RÉSUMÉ OF CASE I

As we view this record it appears to include the following:

1. Premature auricular systoles caused by re-entry from a bypass within the A-V node, giving rise to fixed coupling.

2. Blocking out of all but one of these premature systoles within the A-V junctional tissue because they reached this region when it was absolutely refractory.

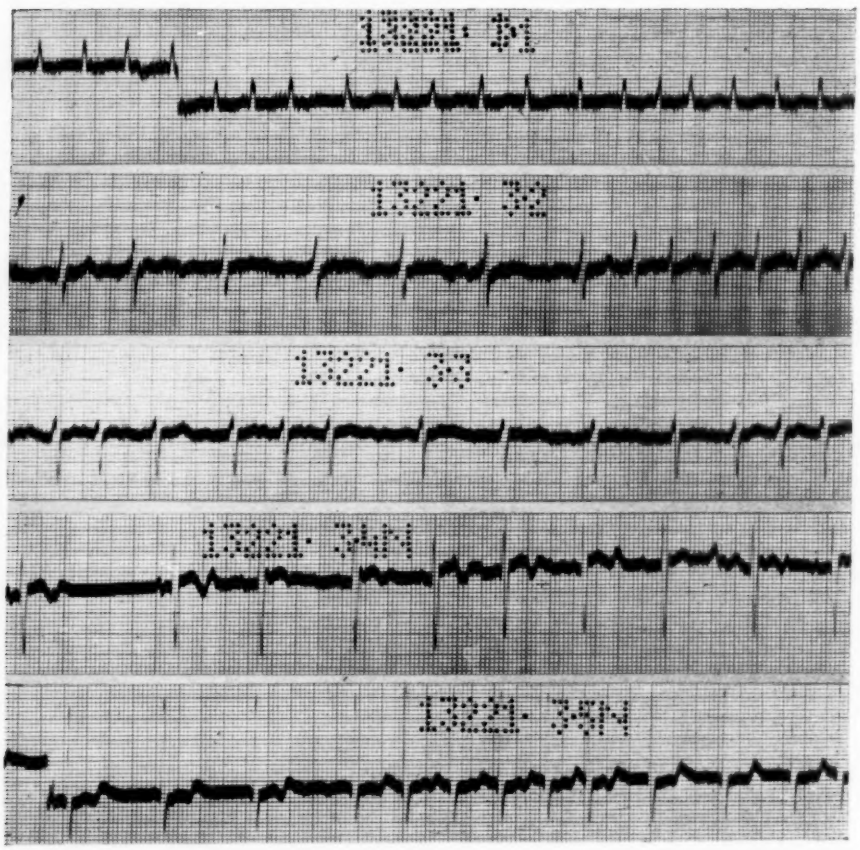

Fig. 4.

3. Interpolation of some of these blocked-out premature systoles, caused by a combination of two factors:

(1) Either (a) the ectopic impulse was slightly delayed in reaching the sinus node, which it ordinarily discharged 0.05 sec. prematurely, a delay sufficient to permit the sinus node to discharge on time, or (b) there was an intermittent, unidirectional, "protection" block around the sinus node, and

(2) the refractory period of the auricles was unusually short, permitting them to respond 0.15 sec. after a previous stimulation.

The importance of local variations in the refractory phase in the pathogenesis of complex arrhythmias is clearly indicated by this unusual record. This record also serves to show that careful analysis is essential for the interpretation of complex arrhythmias.

CASE II. "FOCAL" INTRAVENTRICULAR BLOCK

The second case is one in which the QRS was found to be prolonged beyond 0.12 sec. only in Lead CF_2 (4), in a routine five-lead record, including, also, Lead CF_4 (5); in the other leads its duration was 0.08 to 0.10 sec. (Fig. 5). This patient, a 54-year-old man, had had an attack of precordial pain of approximately one hour's duration five days before the electrocardiogram was taken. The record was repeated on two successive days, and showed this same peculiarity.

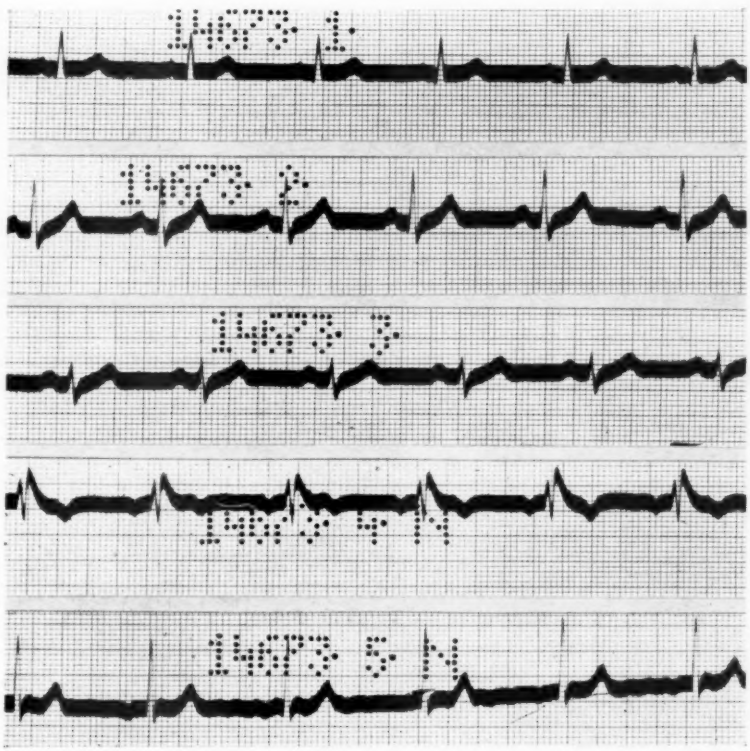

Fig. 5.

The distribution of the precordial area over which the prolonged QRS was present was ascertained by exploring more than fifty points on the chest, using the left leg as the "indifferent" point, and connecting it to the chest electrodes in the manner recommended by the special American Heart Association Committee.

Fig. 6 is a diagram of the chest, with one cycle of the electrocardiograms so obtained mounted over representative areas. To make Leads II and III comparable to the chest leads, inverted images of these two conventional leads were made, and these were placed over the right and left shoulders, respectively.* Electrocardiograms made from peripheral portions of the chest (Fig. 6) were normal, with a QRS of normal duration. As the center of the front of the

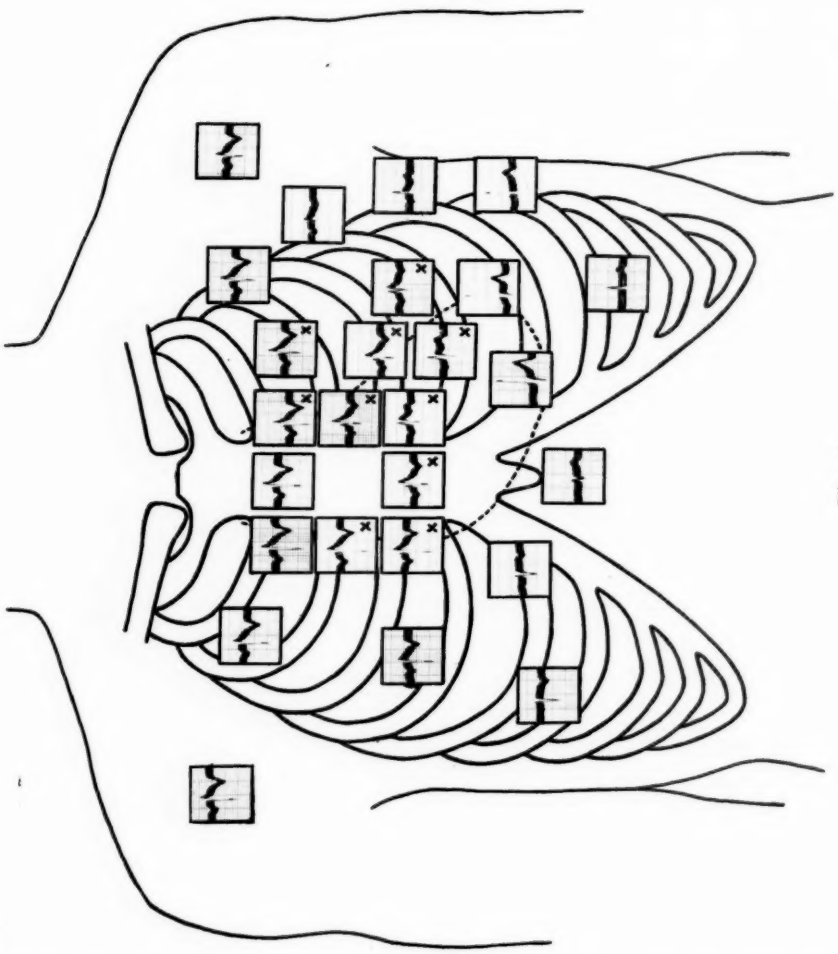

Fig. 6.

chest was reached the QRS became abnormal. The abnormality consists of an M-shaped, mainly inverted QRS which is prolonged, reaching a maximum duration of 0.16 sec. at the level of the fourth intercostal space in the midsternal line. The prolongation of QRS is confined to a small area centering around this point. The curves show-

*This indicates the similarity of these limb leads to chest leads. If the exploring electrode used in taking chest leads is placed on a shoulder, leaving the "indifferent" electrode on the left leg, one obtains an inverted image of Lead II or Lead III, which resembles closely the contour of the chest leads in the region adjacent to the shoulder.

ing this prolongation of QRS are marked with an *X*, and transitions to those points where QRS is normal in appearance and duration are seen. It is interesting to note that CF_2 is in the abnormal area, but CF_4 is not.

The presence of such a prolongation of QRS in any lead indicates intraventricular block, for it shows that the time consumed in activating the ventricles is prolonged, which is the cardinal sign of intraventricular block. However, the region in which this delay occurs here is small, so that the magnitude of the electrical field which it creates, according to the views developed in this laboratory,[1] is also small. Only when the exploring electrode gets close to this area of "focal" intraventricular block will a potential be established sufficient to cause a prolonged initial deviation of the recording galvanometer. At points further from this focal area of block the potential is not large enough to prolong the initial deviation of the galvanometer. In this respect, the mechanism is no different from that seen when S-T deviation in some cases of recent infarction of the anterior wall of the heart is limited to a few precordial leads only.

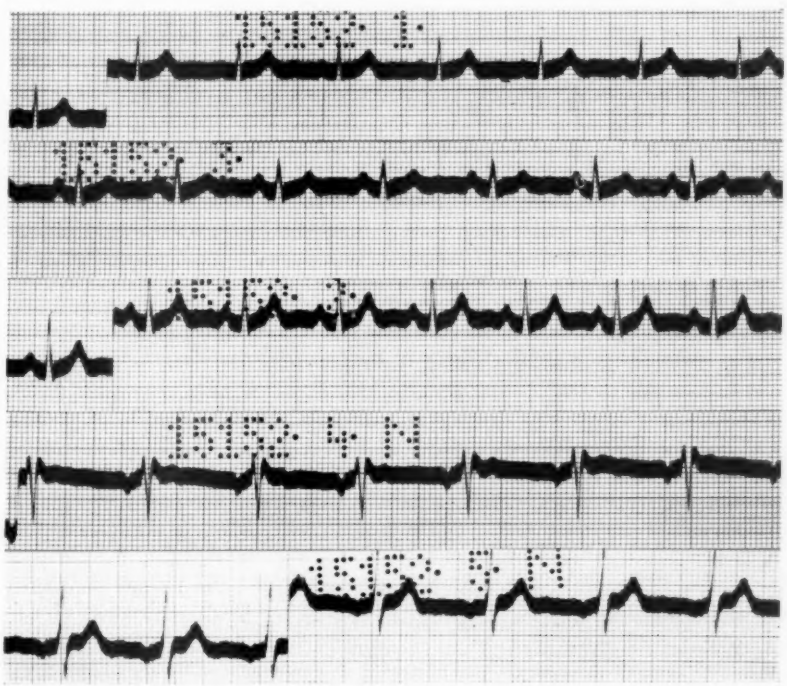

Fig. 7.

The occurrence of "focal" intraventricular block in this case suggests that if multiple chest leads were taken in more cases, other instances of "focal" intraventricular block might be discovered. This case shows further that even the QRS duration is not always an invariant which is independent of the lead used.

The manner in which "focal" intraventricular block was produced in this case is unknown, but it would appear that a lesion involving one of the branches of the right bundle branch, which carries the impulse to the anterior wall of the right ventricle, might cause delay in the spread of the impulse in this region.

The occurrence of prolongation of the QRS complex in only a limited number of chest leads constitutes evidence in favor of the field theory which we have developed,[1] and is not easily reconciled with the theory of vectors, as developed by many of Einthoven's followers.

RÉSUMÉ OF CASE II

Prolongation of QRS confined to certain chest leads indicates "focal" intraventricular block.

SUMMARY

Two unusual cases are presented: In the one there were interpolated, blocked-out, auricular premature systoles, and, in the other, there was "focal" intraventricular block.

We are indebted to Dr. Sidney Strauss and Dr. James Patejdl for permission to report these cases.

Since this communication was sent to press, we have had another case of "focal" intraventricular block in which the abnormal prolongation of QRS was found in the same area as in the above case. Note (Fig. 7) that the prolongation of QRS occurs only in Lead CF_2.

REFERENCE

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THE IMMEDIATE EFFECTS OF THE INTRAVENOUS ADMINISTRATION OF NEOARSPHENAMINE ON THE ELECTROCARDIOGRAM IN CASES OF SYPHILITIC AORTITIS

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In 1932, Wilson[1] reported five cases of late syphilis of the aorta in which conspicuous changes in the electrocardiogram developed following the administration of arsphenamine and related compounds. In the first case, observed in 1919, the electrocardiogram which was taken several days before treatment showed left bundle branch block. A few hours after the first and only intravenous injection of arsphenamine (0.2 Gm.), there were remarkable changes in the cardiac mechanism and in the form of the ventricular deflections. On the following day this patient became semicomatose; the congestive failure increased, and he died four days later. In the second patient, whose electrocardiogram had been previously normal, deep inversion of the T deflection in Lead I and marked left axis deviation, together with aggravation of cardiac pain, occurred after he received three injections of arsphenamine (0.3 Gm., 0.45 Gm., and 0.6 Gm., at intervals of five days and one day, respectively). In a third case, 0.3 Gm. and 0.4 Gm. of arsphenamine were given intravenously on two successive days; following each of these treatments the patient had a severe and prolonged attack of substernal pain. Four days later, a third injection of 0.5 Gm. of arsphenamine was given; this was followed by severe pain and persistent tachycardia which lasted about a week. An electrocardiogram which was taken one week after the third injection showed inversion of the T wave in Lead I and left axis deviation (the control record was essentially normal). Similar events occurred in a fourth patient after the administration of neoarsphenamine. In the fifth patient, T-wave changes developed gradually after six doses of tryparsamide (2 to 3 Gm. each) had been given. In three other patients with syphilitic aortitis no effects on the electrocardiogram were observable after intensive treatment with arsphenamine, nor were there any electrocardiographic changes in twenty cases of primary and secondary syphilis after a course of arsphenamine. Since Wilson's report, no observations of a similar nature have been reported in the literature.

In order to throw further light on the effect of neoarsphenamine in cases of syphilitic aortitis with aortic insufficiency, with or without

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aneurysm or narrowing of the ostia of the coronary arteries, this study was undertaken. Our object was, first, to see whether or not we could confirm Wilson's findings and, second, to ascertain whether electrocardiographic changes, if present, are immediate or delayed, and whether they are of a transient or persistent nature.

MATERIAL AND METHOD

Twenty-two patients with unequivocal evidence of syphilitic aortitis with aortic insufficiency were included in this study. Fifteen of them were patients in this hospital; the rest were ambulatory. The cases were not selected, except that patients with marked congestive failure who did not respond to medical treatment were not studied. All were male patients, ranging in age from 32 to 58 years (mean age, 46). The approximate duration of their syphilis, according to the history, varied from seven to thirty years (mean duration, twenty years). All patients had detailed histories and physical examinations, and all except four had roentgenologic examinations, which included teleoroentgenograms and fluoroscopic studies. In patients suspected of having congestive heart failure, the venous pressure was measured by the direct method,[2] and the arm-to-tongue circulation time was determined by the saccharin method.[3] Substernal or precordial pain and congestive heart failure were graded +, ++, and +++. One-plus heart failure corresponds to class 2a, two-plus to class 2b, and three-plus to class 3 in the scheme of classification of the functional capacity of cardiac patients adopted by the American Heart Association.[4] The blood Wassermann reaction was performed according to the Kolmer technique. The usual three leads of the electrocardiogram were taken on each patient at his first or second visit, using the string galvanometer (Hindle). In several cases, Lead IV, with the left-leg electrode applied just lateral to the site of the apical impulse, and the right- or left-arm electrode applied to the left leg, was the taken before and after the neoarsphenamine injection. In all cases the skin resistance was low (usually about 1000, and always below 2000, ohms), and the string was accurately standardized. The skin resistance was easily kept low by using the new electrocardiographic paste described in 1935 by Jenks and Graybiel.[5] This we employed throughout the period of study.

The diagnosis of syphilitic aortitis in each case was beyond any reasonable doubt. In all of the cases aortic insufficiency was present; in four there was also an aneurysm of the ascending aorta or of the aortic arch, and in twelve there were, in addition, clinical and electrocardiographic findings pointing to varying grades of narrowing of the orifices of the coronary arteries. Twelve of our patients had variable degrees of congestive heart failure. When the functional capacity of a patient was in class 3, the usual treatment for congestive heart failure was instituted until his capacity rose to class 2b, or preferably to 2a. Patients in classes 2a and 2b were also treated for cardiac insufficiency before antisyphilitic treatment was started. At the time of the initial treatment with neoarsphenamine, the functional capacity of the patients fell in class 1, 2a, or 2b. In all cases the dose of neoarsphenamine was small, varying from 0.05 Gm. to 0.3 Gm. All patients except one received neoarsphenamine during this study. The treatment was promptly stopped for a period of time, or the dosage reduced, when any patient showed aggravation of symptoms or significant electrocardiographic changes.

In addition to the control electrocardiograms, which varied in number from one to several for each subject, an electrocardiogram was taken on each of the patients about half an hour before the intravenous injection of neoarsphenamine; this was repeated about four hours after treatment (the interval varied from

three to four hours). The electrocardiogram was repeated just before, and about four hours after, each of the subsequent weekly treatments. Such an examination was usually made three or four times (five, only once; one, five times; and another, seven times). Altogether, sixty-one series of examinations before and after treatment were made in the twenty-two cases, besides the initial and follow-up records. Any significant change in the electrocardiogram within a period of four hours may be reasonably ascribed to the effect of treatment on the pathologic process in the aorta or the heart. If there was any change in the clinical condition of the patients, this was, of course, noted.

RESULTS

It may be of interest to note that abnormalities of the ventricular complex of the electrocardiogram were present in the control record in every one of this series of cases of syphilitic aortitis before any treatment, such as digitalis or antisyphilitic drugs, was begun. These abnormalities consisted of low, flat, or inverted T deflections in the significant leads, depression of R-T or S-T segments amounting to one-tenth of a millivolt, or more, prolongation of the QRS interval (from 0.11 second to complete bundle branch block), and left axis deviation. These abnormalities, except the last, suggest coronary insufficiency caused by encroachment on the ostia of the coronary arteries by the syphilitic process in the first portion of the aorta.[6]

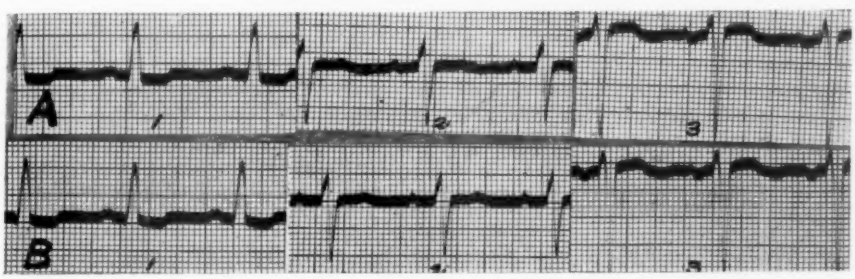

Fig. 1, Case 7.—Electrocardiogram taken just before, *A*, and four hours after, *B*, intravenous injection of 0.05 Gm. of neoarsphenamine.

Out of the sixty-one series of electrocardiograms which were taken just before, and four hours after, the intravenous arsenical therapy in twenty-two cases (neoarsphenamine in all patients except one, who received tryparsamide), there was no abnormality after treatment in fifteen cases. Mild or moderate change in the R-T or S-T segments, or in the T deflections, occurred eleven times out of sixteen such examinations in five cases. In these cases the alterations consisted either of a lowering of the R-T or S-T segment in one or two leads (two cases), or of a flattening or inversion of the T wave or a deepening of previously inverted T waves (three cases). These changes, though not marked, were probably significant in view of the fact that they occurred so soon after the control records (Figs. 2 and 3). The remarkable changes which impressed us particularly, however, occurred in only two patients (cases No. 16 and 20). In these two cases the

records taken four hours after intravenous therapy showed a marked change in the ventricular complex of the electrocardiogram, involving in both cases a depression of the S-T segments and an inversion of previously upright T deflections (Figs. 4 and 5). The changes in

Fig. 2. Case 14.—Electrocardiogram taken just before, *A*, *C*, and four hours after, *B*, *D*, the first two weekly intravenous injections of neoarsphenamine, each of 0.2 Gm. Note the slightly deeper S-T segment in Leads II and III after the first injection, and similar change in Leads I and II after the second injection.

Fig. 3. Case 21.—Electrocardiogram taken just before, *A*, *C*, and four hours after, *B*, *D*, the first two weekly intravenous injections of neoarsphenamine, each of 0.2 Gm. Note the deeper T deflection in Leads I and II and taller T in Lead III after the first injection, and similar changes after the second injection.

these two cases were almost identical, and not unlike those observed after coronary thrombosis or during an attack of angina pectoris. In both they occurred only once during this study. In one (Case 20), the P-R interval lengthened from 0.16 second before injection to 0.20 second after injection, and the marked abnormality in the QRST complex had disappeared a week later. In the other (Case 16), this

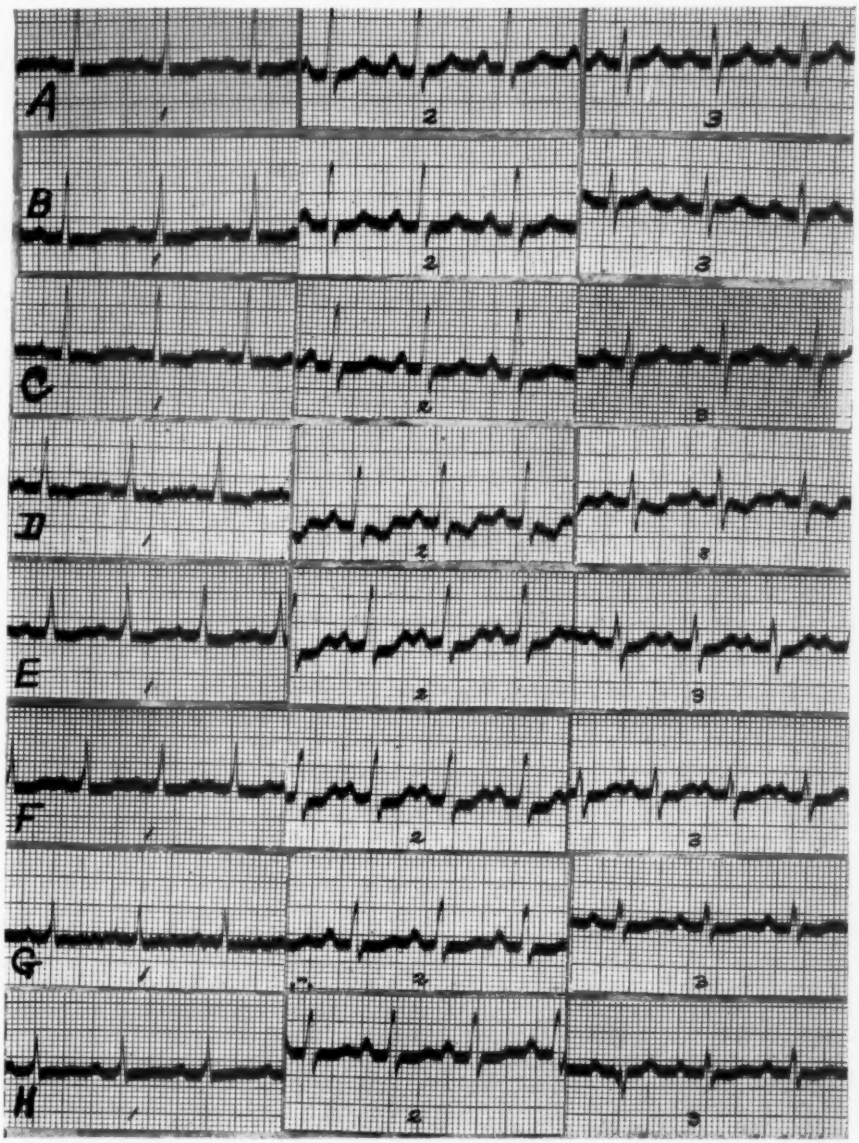

Fig. 4, Case 16.—*A*, Electrocardiogram taken Sept. 15, 1938, just before the commencement of treatment. *B*, Electrocardiogram taken four hours after the first injection of 0.1 Gm. of neoarsphenamine. *C*, Electrocardiogram taken Oct. 16, just before, and *D*, four hours after, the third injection of 0.1 Gm. of neoarsphenamine. Note the marked change in the S-T segment in Leads II and III after injection. *E*, taken on Oct. 20, just before, and *F*, four hours after, the fourth injection. The electrocardiogram was still normal. *G* and *H*, taken before and after the fifth injection on Nov. 3.

abnormality persisted for at least two weeks, and a trace of it was present in a record taken four weeks later. This patient developed a dull precordial pain, which he had never complained of before, and had more shortness of breath a few days after the occurrence of the electrocardiographic changes; the other complained of an aggravation of his precordial pain, with radiation to the left arm for two days after each of these two treatments (the electrocardiographic change occurred after the second). The ultimate result, however, in these two cases was good; both patients showed marked improvement after prolonged treatment with neoarsphenamine, alternating with bismuth.

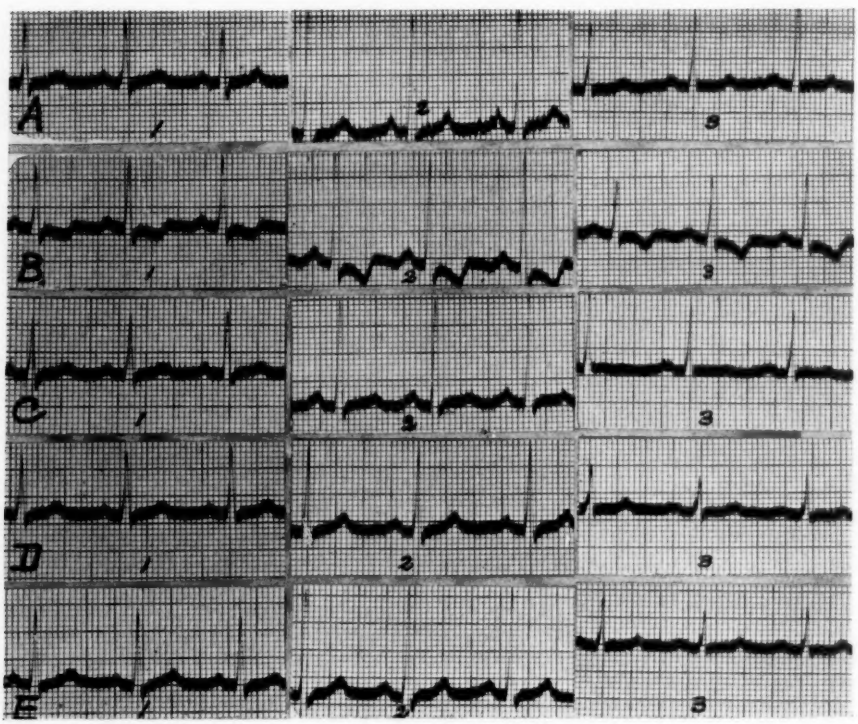

Fig. 5, Case 20.—Electrocardiogram taken Dec. 16, 1937, just before, *A*, and four hours after, *B*, the second injection of 0.3 Gm. of neoarsphenamine (fourth course of treatment). Note the deep inversion of the T deflection in all leads and slight depression of the S-T segment in the first two leads, after this injection. These changes did not recur with subsequent treatments. *C*, Electrocardiogram repeated Dec. 23, without treatment. *D*, Electrocardiogram taken Dec. 28, before and *E*, four hours after, the third injection of 0.2 Gm. of neoarsphenamine.

In this connection it should be mentioned that in one case (Case 19) an apparently spontaneous, but marked, alteration in the electrocardiogram occurred before any treatment was started. The first record showed normal mechanism and left axis deviation, and the second, made fourteen days later, just before treatment, showed left bundle branch block (Fig. 6). Although he was not observed in our hospital, the patient insisted that he did not receive any treatment

during this period. In this case the change must be considered as spontaneous in nature, and not related to any treatment. It may be noted that such a spontaneous change was not observed in any of the other cases in this series.

DISCUSSION

It is not our intention to draw from this study generalizations in regard to the treatment of late syphilis of the cardiovascular system. Suffice it to say this subject is still an open one, and that the precise indication for neoarsphenamine in the therapy of syphilitic aortitis is still controversial.[7, 8, 9, 10, 11] We do wish, however, to emphasize, first, the fact that clinical and electrocardiographic evidences of involvement of the mouths of the coronary arteries were seen in the majority of our cases of advanced syphilitic aortitis. Furthermore, spontaneous changes in the electrocardiogram may occur rarely in such patients, probably as a result of extension of the intimal proliferation in the aorta. Finally, more or less significant changes in the ventricular complex, suggesting interference with the coronary circulation, were observed in the electrocardiograms taken within a few hours after the intravenous treatment in about one-third of the cases in this series. Associated

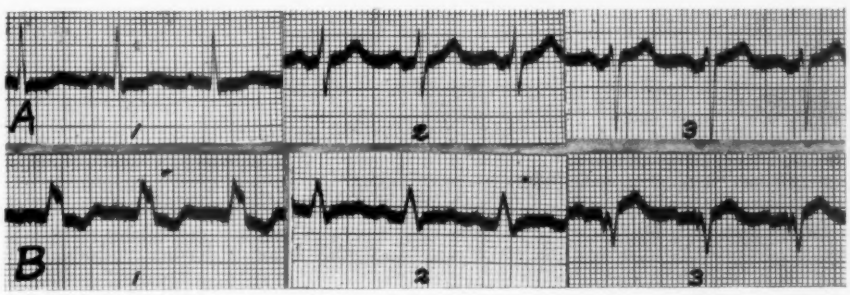

Fig. 6, Case 19.—*A*, Electrocardiogram taken Nov. 6, and *B*, taken Nov. 20, 1936, before any treatment was started. The change appeared to be spontaneous.

with the electrocardiographic changes, there was often also an aggravation of either cardiac pain or pulmonary congestion. From these observations it would be indeed difficult not to suspect that the intravenous neoarsphenamine therapy was in some way related to these changes. Stated in another way, this study serves as a warning that, if used indiscriminately, the intravenous injection of neoarsphenamine may jeopardize, at least temporarily, the coronary circulation, and possibly the life of the patient. We deliberately said *intravenous* neoarsphenamine therapy, for the route of administration may be just as important as the particular drug employed, because with the intravenous route the therapeutic agent is at once delivered into the circulation in its maximal concentration.

Wilson[1] advanced two possible explanations for the electrocardiographic changes observed after treatment. The first assumes that soon

TABLE I

SUMMARY OF CLINICAL, LABORATORY, AND ELECTROCARDIOGRAPHIC OBSERVATIONS IN 22 CASES OF SYPHILITIC AORTITIS BEFORE AND AFTER TREATMENT WITH NEOARSPHENAMINE

CASE, SEX, AGE	DURATION OF SYPHILIS, YEARS	CLINICAL DIAGNOSES	SUBSTERNAL PAIN	CONGESTIVE FAILURE	BL. WASS. AND KAHN	SPINAL FLUID WASS.	EKG. BEFORE TREATMENT	NEOARSPHENAMINE INTRAVENOUSLY GM. PER DOSE	NO. EKG. SERIES (BEFORE AND AFTER INJECTION)	IMMEDIATE EFFECTS ON EKG.	REMARKS
1 M 55	29	*Syphilitic aortitis, aortic, insuff., narrowing coronary ostia, cardiac enl. and insuff.	++	++	+++	Neg.	N.M.† Inverted $T_{1,2}$ Depressed R-$T_{1,2}$	0.2	4	Further depression of R-$T_{1,2}$ after each of the first three treatments	No reaction
2 M 57	25	*Syphilitic aortitis, aortic insuff., aneurysm aortic arch	0	0	+++	Neg.	N.M. Low T_1	0.2	3	0	No reaction
3 M 44	26	*Syphilitic aortitis, aortic insuff., narrowing coronary ostia	+++	0	++	Neg.	N.M. QRS 0.11 sec.	0.1	3	0	No reaction
4 M 38	15	*Syphilitic aortitis, aortic insuff., aneurysm asc. aorta, cardiac enl.	0	0	+++	Neg.	N.M. Low $T_{1,2}$	0.05-0.1	3	0	No reaction
5 M 54	25	*Syphilitic aortitis, aortic insuff., cardiac insuff.	0	+++	+++	Neg.	N.M. Flat T_1 Low $T_{2,3}$	0.05-0.1	3	Moderate depression R-T_2 after third injection (0.1 Gm.)	Died 3½ mo. later of congestive failure

Note: Asterisks denote detailed roentgenologic examinations.
†Normal mechanism.

6 M 54	?	*Syphilitic aortitis, aortic insuff., aneurysm aortic arch, narrowing coronary ostia, cardiac enl.	++	0	+++	Neg.	N.M. L.A.D.‡	0.1	1	0	No reaction
7 M 47	?26	*Syphilitic aortitis, aortic insuff., narrowing coronary ostia, cardiac enl. and insuff.	++	0	++	Neg.	N.M. Partial Lt. BBB§ Vent. extrasystole	0.05	2	0	No reaction. Died at home 3 weeks later
8 M 54	31	*Syphilitic aortitis, aortic insuff., narrowing coronary ostia. Amebic and bac. dysentery	++	0	+++	+++	N.M. L.A.D. Flat $T_{1, 2, 3}$	0.2	4	0	No reaction. Died from dysentery; autopsy
9 M 33	?10	*Syphilitic aortitis, aortic insuff., narrowing coronary ostia, aneurysm asc. aorta	+++	0	++	Neg.	N.M. L.A.D.	0.05-0.1	3	0	No reaction
10 M 50	23	*Syphilitic aortitis, aortic insuff., cardiac enl. and insuff.	++	+++	++	Not exam.	N.M. Flat T_1, low T_2 Inverted T_3 L.A.D.	0.2	3	0	No reaction. Died 4 weeks later of congestive failure
11 M 52	?11	*Syphilitic aortitis, aortic insuff., cardiac enl. and insuff.	0	++	+++	+++	N.M. Inverted $T_{2, 3}$	0.1	2	0	No reaction
12 M 47	23	*Syphilitic aortitis, aortic insuff., narrowing coronary ostia, cardiac enl. and insuff.	++	+++	++	Neg.	N.M. L.A.D.	0.05	1	0	Improved after hospitalization. Apparently worse after this injection, and died 48 hours later of congestive failure and angina

‡Left axis deviation.
§Bundle branch block.

TABLE I—CONT'D

CASE, SEX, AGE	DURATION OF SYPHILIS, YEARS	CLINICAL DIAGNOSES	SUBSTERNAL PAIN	CONGESTIVE FAILURE	BL. WASS. AND KAHN	SPINAL FLUID WASS.	EKG. BEFORE TREATMENT	NEOARSPHENAMINE INTRAVENOUSLY GM. PER DOSE	NO. EKG. SERIES (BEFORE AND AFTER INJECTION)	IMMEDIATE EFFECTS ON EKG.	REMARKS
13 M 45	21	*Syphilitic aortitis, aortic insuff., cardiac enl. and insuff.	0	+++	++	Neg.	N.M. Diphasic T_1 Inverted $T_{2, 3}$	0.05	1	0	No reaction
14 M 42	22	Syphilitic aortitis, aortic insuff., juxta-articular nodules. Hypertension, cardiac enl. and insuff.	0	+++	+++	Not exam.	N.M. Low $T_{1, 2, 3}$	0.2	3	Deeper inversion $T_{2, 3}$ after first 2 injections	Condition worse after first injection. Patient refused treatment after the third. Died 2½ months later
15 M 43	15	Syphilitic aortitis, aortic insuff., narrowing coronary ostia, cardiac enl. and insuff.	+	++	+++	Neg.	N.M. Flat T_1 Sharply inverted $T_{2, 3}$	0.1	3	0	Died 3 months later of congestive heart failure
16 M 38	20	*Syphilitic aortitis, aortic insuff., cardiac enl. and insuff.	0	+++	+++	Neg.	N.M. Diphasic T_1	0.1	5	After third injection, marked depression of ST segment and inversion of $T_{2, 3}$	Developed dull precordial pain and more dyspnea several days after this injection. Ultimately patient's condition became much improved, and he was ambulatory with practically no congestive failure (May 25, 1939)

17 M 57	30	Syphilitic aortitis, aortic insuff., cardiac enl. and insuff., tabes dorsalis	0	+	++	++	N.M. Low $T_{1, 2}$ Inverted T_3	Trypars-amide 0.5	1	0	No reaction
18 M 39	13	Syphilitic aortitis, aortic insuff., cardiac enl.	0	0	+	Not exam.	N.M. Inverted $T_{2, 3}$ L.A.D.	0.2	3	After first inj., T_1 became inverted, $T_{2, 3}$ slightly deeper. After second $T_{2, 3}$ deeper. After third T_1 flattened, $T_{2, 3}$ sl. deeper	No reaction
19 M 40	20	*Syphilitic aortitis, aortic insuff., narrowing coronary ostia, cardiac enl. and insuff.	+	++	+++	Neg.	N.M. L.A.D. Later Lt. BBB	0.3	1	0	In the afternoon of the day of treatment patient developed feverishness and more substernal pain and dyspnea for 36 hours
20 M 48	22	*Syphilitic aortitis, aortic insuff., narrowing coronary ostia	++	0	++	Not exam.	N.M. L.A.D. Sl. depressed R-$T_{2, 3}$	0.3-0.2	7	After second injection, depression of ST segment and complete inversion of T in all leads	After each of first two treatments, patient developed more precordial pain, with radiation to left arm, for 2 days. Ultimate result good after 17.1 Gm. neoarsphenamine and 5.6 Gm. bismuth tartrate
21 M 58	?25	*Syphilitic aortitis, aortic insuff., cardiac enl., syphilis of CNS, hypertension	0	0	++	Not exam.	N.M. Inverted $T_{1, 2, 3, 4}$	0.2	3	After each of first two injections, $T_{1, 2}$ became deeper	No reaction
22 M 32	7	*Syphilitic aortitis, aortic insuff., narrowing coronary ostia, cardiac enl. and insuff.	++	+	++	Not exam.	N.M. QRS 0.09 sec. Depressed R-$T_{1, 2}$ Notched R_1 and low T_1	0.1	2	0	No reaction

after intravenous therapy there occurs a reaction in the syphilitic aortic lesions at the mouths of the coronary arteries, or a replacement of the active lesion by scar tissue. The second explanation, which was preferred by Wilson, assumes that the effect of arsphenamine therapy upon the myocardial syphilomata may affect the integrity of the heart, directly or indirectly, by interfering with the coronary circulation locally. Since syphilis of the myocardium is rare, and since the changes observed by us simulate those observed in other cases of coronary disease, we believe that these changes were caused by a reaction in the syphilitic aortic lesions, with resulting encroachment on the coronary ostia. The fact that they occurred almost immediately after the intravenous treatment precludes the possibility of replacement by scar tissue as the cause in our cases.

With the ultimate evaluation of the use of neoarsphenamine in the treatment of syphilitic aortitis this article is not concerned. Our observations suggest that neoarsphenamine, when administered in small doses, exerts an immediate effect on syphilitic lesions in the aorta, and that in cases of marked coronary involvement it may exert temporarily a deleterious effect on the coronary circulation.

SUMMARY

In an electrocardiographic study of twenty-two patients suffering from syphilitic aortitis with aortic insufficiency, it was found that significant and marked changes in the ventricular complex of the electrocardiogram occurred in two cases, and minor alterations in five cases, within a few hours after the administration of neoarsphenamine. The possible significance of these observations is discussed.

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RESPONSES OF BLOOD VESSELS IN THE RESTING HAND AND FOREARM TO VARIOUS STIMULI*

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WITH the development of accurate plethysmographic methods, considerable knowledge has been gained regarding blood flow in, and vasomotor reactions of, blood vessels in the hand. However, it has been demonstrated that alterations in blood flow in the hand apparently do not parallel vascular responses elsewhere in the body. For example, Grant and Pearson[1] and, more recently, Kunkel, Stead, and Weiss[2] have reported that adrenalin, although it produces a marked decrease in blood flow through the hand, causes an increase in flow through the forearm. Likewise, Abramson, Zazeela, and Oppenheimer[3] have observed that smoking causes a significant reduction in flow in the hand and practically no change in the forearm. Since blood flow measurements in the hand have been used qualitatively to gauge changes in systemic flow during the state of shock[4] and during the inhalation of various gases,[5] it becomes important to ascertain under what conditions, if any, such assumptions are valid, and whether more reliable information concerning the peripheral circulation may not be obtained from studying other vascular beds.

The present study deals with a comparison of the reactions of blood vessels in the hand and forearm to different types of stimuli. An attempt is made (1) to ascertain the relationship of vascular responses in these two areas to changes in the systemic circulation, (2) to evaluate and clarify the mechanisms responsible for the limb-volume changes produced by these stimuli, and (3) to ascertain whether or not the control of blood flow through the forearm differs from that through the hand.

METHOD

Studies were made on twenty-five subjects who showed no evidence of circulatory disease, on four with benign hypertension, and on one with postural hypotension. In each experiment simultaneous blood-flow studies on a hand and a contralateral forearm were obtained at a room temperature which ranged between 25 and 27° C., and at bath temperatures of 32°, and 42 to 45° C. The blood flow in the hand and forearm was measured according to the technique previously described by one of us,[6] and was calculated in c.c. per minute per 100 c.c. of limb volume. Volume changes were studied by recording the baseline continuously on a slow drum, and were calculated in c.c. of change per liter of limb volume. In

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the case of the forearm, a blood pressure cuff was placed around the wrist and inflated to a pressure of 300 mm. Hg, which was maintained during observations on blood flow or volume changes.

The effect of mental arithmetic, pain, and hyperventilation on blood flow and limb volume was studied in detail, and, in a number of instances, simultaneous changes in pulse rate and arterial blood pressure were also recorded. The mental arithmetic consisted of a problem in multiplication which required between twelve and twenty seconds to solve. Pain was induced by means of pinching, the duration of which varied from a few seconds up to twenty-five seconds, care being taken to maintain the intensity of the pain throughout. The sites generally utilized were the inner surface of the arm, the neck, and the anterior, upper portion of the chest. Hyperventilation was carried out until the patient became quite dizzy, and generally lasted from seventy-five to one hundred twenty seconds. In each trial, sufficient control observations were made before and after the application of the stimulus to establish a cause-and-effect relationship; in addition, the same test was repeated a number of times on each subject, in order to ascertain whether the response was constant.

RESULTS

Effect of a Pinch

Systemic Effects.—In thirteen trials on eight subjects, blood pressure and pulse rate readings were obtained before, during, and after the continuous application of a pinch. In twelve instances there was no significant change in the systolic blood pressure, and either no change, or only a slight increase, in diastolic pressure. In the one exception there was a rise in systolic pressure of 6 to 8 mm. Hg. In eight experiments there was no change in pulse rate, in four there was a slight decrease, and, in one, a significant decrease, i.e., from seventy-eight to forty-eight beats per minute. One of the subjects in the group was suffering from hypertension, while the others were normal. That the stimulus was effective was verified by the fact that characteristic volume changes were produced simultaneously in the forearm.

Changes in the Hand.—*A. Volume:* At a bath temperature of 32° C., pinching produced a definite drop in the baseline, indicating a significant reduction in limb volume, in thirty-five out of thirty-seven experiments. In three of these, the average effect was much greater when the blood flow was found to be normal or increased, as contrasted with results obtained when it was diminished. Of the remaining two experiments, in one there was a questionable response, and, in another, no effect. In both of these cases the initial blood flow in the hand was also found to be low. The reduction in hand volume varied from 0.6 to 20.8 c.c. per liter of limb volume (Fig. 1*A*). At a bath temperature of 42 to 45° C., there was also a decrease in volume in all instances (eleven trials). In one of these, no effect had been produced at 32° C., at which temperature the blood flow was below the normal range, whereas at 45° C. it was normal. The decrease in volume at a bath temperature of 42 to 45° C. varied from 1.1 c.c. to 10.0 c.c. per liter of limb volume. In all instances a greater effect was

obtained when the pinch was prolonged than when it was of short duration.

B. *Blood Flow:* At a bath temperature of 32° C., pinching produced a decrease in the rate of blood flow through the hand in seven out of ten cases. In two there was a questionable effect, and, in one, no effect. The greatest decrease in blood flow produced by a pinch was from 12.8 c.c. (control) to 2.2 c.c. per min. per 100 c.c. of limb volume (Fig. 2). At a bath temperature of 42 to 45° C. there was a decrease in six trials, no effect in one, and a slight increase in another. The greatest decrease in blood flow at this bath temperature was from 52.1 c.c. (control) to 34.8 c.c. per min. per 100 c.c. of limb volume.

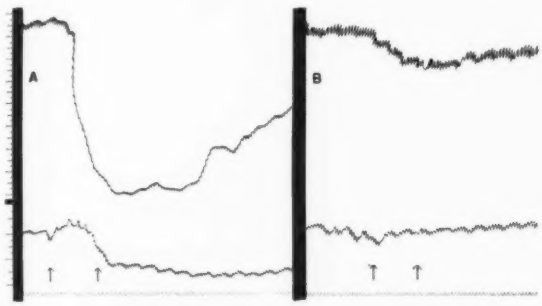

Fig. 1.—Effect of pinch on volume of hand (upper graph) and forearm (lower graph) in subject L.S. *A*, Normal venous pressure. Hand, decrease of 17.3 c.c. per liter of limb volume. Forearm, initial rise of 0.8 c.c. per liter, followed by a decrease of 3.4 c.c. *B*, Pressure of 70 mm. Hg in veins of both extremities produced by the application and maintenance of a similar pressure at the arms. Hand, decrease of 3.3 c.c. per liter of limb volume. Forearm, no effect on limb volume now produced by pinch. Interval designated by arrows indicates duration of application of continuous pinch. Time in seconds. Calibration in 0.25 c.c. Bath Temp.—32° C. Hand volume—445 c.c. Forearm volume—515 c.c.

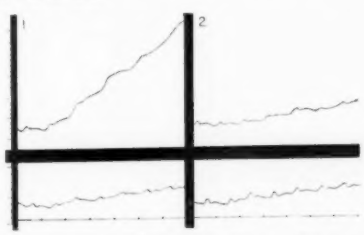

Fig. 2.—Blood-flow changes resulting from the continuous application of a pinch. Upper graph, hand; lower graph, forearm. *1*, Control blood flow. Hand, 12.8 c.c. Forearm, 1.2 c.c. *2*, Blood-flow records obtained during pinch. Hand, 2.2 c.c. Forearm, 1.2 c.c. Time in seconds. Calibrations in 0.25 c.c. All figures represent c.c. per min. per 100 c.c. limb volume. Bath Temp.—32° C.

Changes in the Forearm.—A. *Volume:* At a bath temperature of 32° C., the pinch reflex produced a definite decrease in forearm volume in sixteen experiments, a slight or questionable response in six, no effect in six, and a slight to moderate increase in ten. The decrease in volume varied from 0.3 c.c. to 7.3 c.c. per liter of limb volume (Fig. 1*A*), and the increase from 0.3 c.c. to 3.2 c.c. At a bath temperature of 42 to 45° C., a slight decrease in limb volume was recorded in five instances, no effect in three, and a rise in three.

B. *Blood Flow:* In eighteen of twenty-one trials, pinching produced no change in blood flow in the forearm. In two instances there was a decrease of only 0.4 c.c. per min. per 100 c.c. of limb volume, and in one there was an increase of 0.7 c.c. per min. per 100 c.c. of limb volume. The latter took place at a bath temperature of 45° C. That ineffectiveness of the stimulus could not account for the lack of response was proved by the fact that in most experiments there was a simultaneous decrease in the blood flow to the hand (Fig. 2).

Thus, a pinch generally elicited a decrease both in volume of, and blood flow in, the hand, and the magnitude of the response depended somewhat upon the pre-existing degree of vasomotor tonus. In contrast, the blood flow to the forearm was not altered, while the forearm volume was either decreased, unchanged, or increased.

EFFECT OF MENTAL ARITHMETIC

Systemic Effects.—In nineteen trials on eleven subjects, arterial blood pressure readings and pulse rates were obtained simultaneously with blood flow measurements. In every instance but one there was a significant rise in systolic blood pressure, ranging from 6 to 40 mm., with an average of 14 mm. The greatest effects were produced in two patients who were suffering from benign hypertension. In four trials there was no change in diastolic pressure, whereas in eleven there was a rise ranging from 4 to 16 mm., with an average of 11 mm. The one subject in whom little rise in systolic pressure was evident showed an increase of 12 mm. in diastolic pressure. The pulse rate increased by an average of eleven per minute in five trials, remained unchanged in five, and decreased ten per minute in one. These observations are in contrast with the systemic response to the application of a pinch, during which procedure little or no effect was produced on either systolic or diastolic blood pressure.

Changes in the Hand.—A. *Volume:* At a bath temperature of 32° C., the mental arithmetic caused a decrease in limb volume in twenty-four experiments. This decrease varied in magnitude from 5.2 c.c. to 17.0 c.c. per liter of limb volume (Figs. 3*A*, 4*A*); in one case there was no change. At a bath temperature of 42 to 45° C., there was also a diminution in volume in all experiments (seven trials); this decrease ranged from 2.0 c.c. to 8.2 c.c. per liter of limb volume.

B. *Blood Flow:* At a bath temperature of 32° C., the mental arithmetic produced a significant decrease in blood flow in the hand in seven of eight trials; this decrease varied in magnitude from 3.0 c.c. to 14.8 c.c. per minute per 100 c.c. of limb volume (Fig. 5). In one instance, an increase of 0.9 c.c. per minute per 100 c.c. of limb volume was observed. At a bath temperature of 45° C., no change was produced in the one subject studied.

Changes in Forearm.—A. *Volume:* At a bath temperature of 32° C., the mental arithmetic produced a diminution in limb volume in eight experiments (Fig. 4*A*), a doubtful effect in one, and an increase in seventeen (Fig. 3). The decrease varied from 0.3 c.c. to 8.4 c.c. per liter of limb volume, and the increase from 0.6 to 6.5 c.c.

B. *Blood Flow:* The mental arithmetic produced a significant increase in the rate of blood flow in the forearm in ten trials (Fig. 5), and no effect in two. In one experiment the flow increased from a control value of 3.7 c.c. to 7.3 c.c. per min. per 100 c.c. of limb volume. In most instances the increase in forearm volume and blood flow was accompanied by opposite effects in the hand (Figs. 3 and 5).

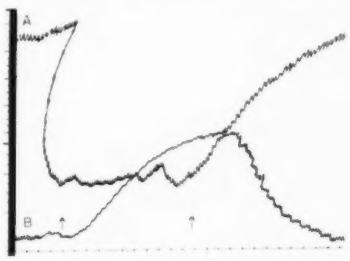

Fig. 3.—Effect of mental arithmetic on limb volume in subject H.C. *A*, Hand, decrease of 10.2 c.c. per liter of limb volume. *B*, Forearm, increase of 4.8 c.c. per liter of limb volume. Interval designated by arrows indicates period in which problem was being solved. Time in 5 sec. Calibrations in 0.25 c.c. Bath Temp.—32° C.

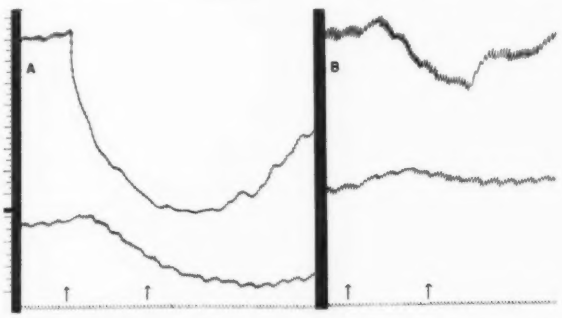

Fig. 4.—Effect of mental arithmetic on volume of hand (upper graph) and forearm (lower graph) in subject L.S. *A*, Normal venous pressure. Hand, decrease of 18.0 c.c. per liter of limb volume. Forearm, initial slight rise, followed by a decrease of 4.8 c.c. per liter of limb volume. *B*, pressure of 70 mm. Hg maintained at both arms during procedure in order to raise venous pressure to same level. Hand, decrease of 5.0 c.c. of limb volume. Forearm, increase of 1.4 c.c. per liter of limb volume. Interval designated by arrows indicates period in which problem was being solved. Time in seconds. Calibrations in 0.25 c.c. Bath Temp.—32° C. Hand volume—445 c.c. Forearm volume—515 c.c.

In summary, mental arithmetic caused a definite reduction in volume of, and blood flow in, the hand. Contrariwise, an increase in blood flow to the forearm generally occurred, while the forearm volume either decreased, or remained unchanged, or, more often, increased.

EFFECT OF HYPERVENTILATION

Systemic Effects.—In eight of eleven subjects whose blood pressure was measured, there was a rise in systolic pressure ranging from 9 to 18

mm. Hg, with an average of 11 mm. In the remaining three cases, no change in systolic pressure was observed. In seven instances there was also a rise in diastolic pressure ranging from 5 to 19 mm., with an average of 11 mm. The diastolic pressure was unchanged in two subjects, and decreased 14 mm. Hg in two. The systolic pressure in these latter two cases remained unchanged. In all instances (fourteen trials) there was an increase in the pulse rate ranging from six to thirty-eight beats per minute, with an average of nineteen.

Volume Changes.—Because of the movements incident to forced respiration, it was not possible to obtain an accurate measurement of the effect upon limb volume. However, in most instances the volume of the hand appeared to decrease, whereas that of the forearm was either unaffected or increased.

Blood Flow.—In all eleven instances there was a significant reduction in blood flow to the hand. In one experiment the blood flow decreased from 16.0 c.c. to 5.0 c.c. per min. per 100 c.c. of limb volume. In the forearm, in all seventeen instances, the flow increased significantly with this stimulus; the greatest effect was observed in one experiment in which the flow rose from 1.8 c.c. (control) to 8.4 c.c. during the period of hyperventilation (Fig. 6). Again, to this type of stimulus, as to the ones already described, the blood vessels in the hand and those in the forearm appeared to respond differently.

EFFECT OF AN ELEVATED VENOUS PRESSURE UPON CHANGES IN LIMB VOLUME

In order to obtain more evidence concerning which blood vessels were involved in the alterations of limb volume, the various stimuli were applied while a venous pressure of 70 to 80 mm. Hg was artificially maintained in the extremities under study. This pressure level was chosen because Lewis[7] has demonstrated that under these conditions the minute vessels of the skin cannot effectively constrict. He showed that if the venous pressure was raised to 80 or 90 mm. Hg, the introduction of adrenalin intracutaneously in man did not produce the characteristic white spot. However, when the pressure was lowered to 40 to 60 mm., the adrenalin effect on the vessels became evident. Further, he has presented considerable evidence to show that the minute vessels which are involved include venules and probably capillaries, but *not* arterioles.

The venous pressure was elevated by applying a cuff pressure of 70 to 80 mm. Hg to the arm just above the elbow. When the volume of the extremity became constant, indicating that the desired pressure in the veins had been reached, pinching was tested in fourteen instances and the effect of mental arithmetic in eleven. It was found that in the hand, in all trials but two, this procedure definitely reduced the magnitude of the response, both to the pinch and mental arithmetic, to about

80 per cent of the control value (Fig. 1). In two instances, the constrictor effect was not altered with either stimulus. In the forearm, with both the pinch and the arithmetic, the decrease in volume was now either slight or no longer apparent; in fact, in some instances a slight increase in limb volume occurred (Figs. 1 and 4). The significance of these observations will be discussed below.

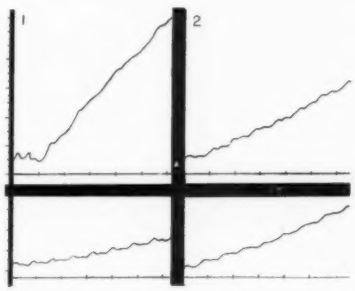

Fig. 5.—Blood-flow changes resulting from mental arithmetic in subject H.C. Upper graph—hand. Lower graph—forearm. *1*, Control blood flow. Hand, 12.0 c.c. Forearm, 1.4 c.c. *2*, Blood-flow records obtained during the period in which problem was being solved. Hand, 5.4 c.c. Forearm, 2.7 c.c. Time in seconds. Calibrations in 0.25 c.c. All figures represent c.c. per minute per 100 c.c. limb volume. Bath Temp.—32° C.

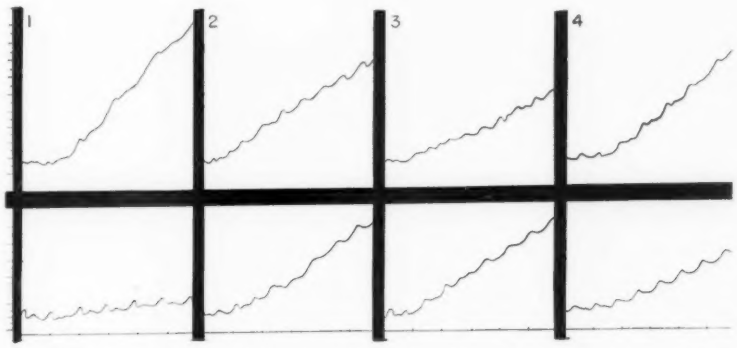

Fig. 6.—Effect of hyperventilation for two minutes and thirty seconds on blood flow in hand (upper graph) and forearm (lower graph) in subject M.M. *1*, Control blood flow. Hand, 16.0 c.c. Forearm, 1.8 c.c. Records *2* and *3* taken during period of hyperventilation. *2*, eighty seconds after onset. Hand, 10.0 c.c. Forearm, 8.4 c.c. *3*, 100 seconds after onset. Hand, 7.0 c.c. Forearm, 7.2 c.c. *4*, ten seconds after termination of period of hyperventilation. Hand, 12.3 c.c. Forearm, 6.0 c.c. Time in seconds. Calibrations in 0.25 c.c. All figures represent c.c. per minute per 100 c.c. limb volume. Bath Temp., 32° C.

RELATIVE PROPORTION OF SKIN AND MUSCLE IN THE HAND AND FOREARM

Since the responses to the various stimuli were found to be different in the hand and forearm, it was thought necessary to ascertain whether or not the apparent variations could in any way be correlated with the different proportions of skin, muscle, and bone which are present in these two regions. Accordingly, three hands and three forearms, obtained at autopsy, were dissected, and the weight and displacement volume of each of the tissues ascertained. The portions of the extremities studied were equivalent to the parts included in the dif-

ferent plethysmographs during blood-flow measurements. With the type of apparatus used by us, the average volume of the forearm was 550 c.c., and that of the hand, 435 c.c. The data in Table I reveal that skin and subcutaneous tissue comprise 30.2 per cent of the hand volume and 13.4 per cent of the forearm volume; whereas muscle forms 15.5 per cent of the hand and 58.6 per cent of the forearm. The average forearm segment (550 c.c.) will then contain a total of about 74 c.c. of skin and 322 c.c. of muscle, and the hand segment (435 c.c.), 131 c.c. of skin and 67 c.c. of muscle. It is of interest that the forearm segment consists of about 56 per cent as much skin as does the hand.

TABLE I

RELATIVE QUANTITIES OF SKIN, MUSCLE, AND BONE IN HAND AND FOREARM

TISSUE	HAND		FOREARM	
	AV. % BY WT.	AV. % BY VOL.	AV. % BY WT.	AV. % BY VOL.
Skin—subcutaneous tissue	28.0	30.2	12.0	13.4
Muscle	15.0	15.5	57.0	58.6
Bone plus fat and tendon	57.0	54.3	31.0	28.0

DISCUSSION

Blood Flow Responses in the Hand and Forearm.—The above data corroborate previous studies,[4, 8] which demonstrated that a stimulus like pain, for example, can greatly diminish blood flow in the hand without significantly altering the systemic circulation. It is clear that since the changes in flow with this type of stimulus are abolished by sympathetic paralysis,[4, 9] they must be brought about by alterations in the tonus of the vasomotor system. Blood flow to the hand is also decreased by performing mental tasks (Fig. 5), epinephrine administration,[1, 2] and hyperventilation (Fig. 6), all of which generally increase peripheral blood pressure, pulse rate, and probably cardiac output. It has been implied that the central vasomotor control of those vessels of the hand which are responsible for the vasoconstrictor effects can be largely negated by raising the local temperature to 42 to 45° C.[2, 6, 8] However, our results indicate that in most subjects, if the stimulus is sufficiently strong, a definite decrease in blood flow through the hand will consistently take place even under these conditions.

In sharp contrast to that in the hand, our studies indicate that blood flow in the forearm is not diminished by any of the stimuli used. It is generally unaffected by stimuli which do not significantly alter the pulse rate or blood pressure (pinch), and is definitely augmented by those which increase systemic blood flow (epinephrine,[2] mental arithmetic, hyperventilation). It would appear, therefore, that, in contrast to the hand, blood flow, and hence arteriolar tonus, in the forearm is not significantly influenced by the vasomotor system.

Factors Involved in Changes in Limb Volume.—It is clear that a transient diminution in limb volume may be caused either by a relative decrease in inflow to the part, or by a relative increase in outflow. A decrease in inflow might occur passively as a result of diminished peripheral blood pressure, or actively because of arteriolar* constriction. An increased outflow might likewise result passively from a decreased venous pressure in the large veins proximal to the extremity, or actively from local constriction of the venous bed.† Conversely, an increase in limb volume may result from a passive or active dilatation of arterioles, or from a passive or active dilatation of the venous bed.

A. Increase in Limb Volume: In the present study, an increase in limb volume was rarely if ever encountered in the hand, but often seen in the forearm, especially during the solution of a problem in mental arithmetic (Fig. 3). This could not have been produced by a local, passive, venous distention resulting from a rise in central venous pressure, because it was found that the latter was not affected by the stimuli. The fact that the increase in forearm volume was coincidental with an increase in blood flow through the forearm (Fig. 5) suggests that it may have been caused, in part at least, by arteriolar dilatation. Further, in view of the associated rise in blood pressure, it seems reasonable to assume that the dilatation was primarily *passive* in nature. It should be mentioned, however, that in some instances slight increases in flow and volume occurred in the absence of any discernible increase in arterial pressure; and, furthermore, that there was not always an exact parallelism between changes in blood pressure and in blood flow and limb volume. The possibility exists, of course, that in these instances the auscultatory method may have failed to detect slight alterations in mean blood pressure. Nevertheless, the possibility of *active* arteriolar dilatation of slight degree cannot be ruled out.

B. Decrease in Limb Volume: The diminished limb volume in both the forearm and hand was obviously not the result of a decreased systemic flow, inasmuch as none of the stimuli significantly reduced the pulse rate or blood pressure. That more rapid drainage from the limb, as a result of a decrease in central venous pressure, does not play a role is indicated by the fact that a response of the same magnitude occurred when the pressure in the veins was maintained artificially at 10 to 20 mm. Hg.

Since the blood flow in the hand was generally reduced by the stimuli which we employed (Figs. 2, 5, 6), it is apparent that active constriction of arterioles was responsible, in part, at least, for the

*By arterioles we mean those small vessels which have sufficient muscle tone to contribute to peripheral resistance in a physiologic sense. They include arteriovenous shunts, which are referred to subsequently.

†By venous bed we mean all small vessels which do not offer a significant amount of peripheral resistance under physiologic conditions. They include those vessels which cannot constrict against an internal pressure of 70 mm. Hg, such as veins, venules, and capillaries.

diminution in hand volume. The fact that a venous pressure of 70 mm. Hg, which was sufficient to nullify any increase in venous tonus, did not entirely abolish the effect in the hand (Figs. 1, 4) is further proof that there was arteriolar constriction. At the same time, since there was a decrease of about 80 per cent in the response, it is probable that venous constriction played a major role in diminishing the volume of this limb.

In the forearm, as has been stated before, the diminution in volume was rarely accompanied by a decrease in blood flow (Figs. 2, 5). Furthermore, this diminution in forearm volume was almost completely abolished when the venous pressure was artificially raised to 70 mm. Hg (Figs. 1, 4). It follows, therefore, that in the forearm the stimuli produced little, if any, constriction of arterioles, and that the phenomenon was almost entirely the result of active venous constriction, whereas, in the hand, both factors played a role. With respect to the venous constriction, it is probable that the venous beds of both the hand and forearm react alike to vasomotor impulses.

The results of our studies on the forearm are clear-cut examples of a decrease in volume without any change in blood flow, and show that volume changes of a limb or organ do not necessarily indicate that a change in blood flow has occurred. This fact should be stressed because, in the past, it has been tacitly implied or assumed that such volume changes do reflect changes in flow. The results also suggest that the venous portion of the circulatory system, in the forearm, at least, can be acted upon by central vasoconstrictor impulses independently of effects upon the arterioles. In view of this, it is apparent that the vascular bed of the resting forearm is well adapted to the study of the physiologic responses of the venous portions of the peripheral circulation.

Factors Accounting for Differences in the Vascular Responses of the Hand and Forearm.—The results of our studies of volume changes of the hand are in agreement with those of Capps,[8] who is of the opinion that the alterations in hand volume induced by painful stimuli are caused, in part, at least, by changes in venous tonus. Kunkel, Stead, and Weiss,[2] in a recent study which included investigation of the reflex volume changes in both the hand and forearm, did not attempt to distinguish between arterioles and venules. They concluded that the decrease in volume was caused by active vasoconstriction, and that the small vessels of the hand and forearm were qualitatively alike in their response to vasomotor impulses. Our observations with regard to limb volume changes are essentially the same as theirs. However, when the limb volume alterations are considered together with blood-flow changes, it becomes apparent that there is a real difference between the composite vasomotor reactions of the small vessels of the hand and those of the forearm. For, as has been stated above, the arterioles in the hand respond to all of the

stimuli used in this study by constricting, whereas those in the forearm are either not affected or actually dilate.

The question arises whether the differences in vascular response in the hand and forearm can be explained by the fact that their relative content of muscle and skin is not the same, or by differences in the reactions of skin vessels. Although that part of the forearm which was studied is largely muscle, it does contain about 56 per cent as much skin as that enclosed in the hand plethysmograph, an amount large enough to allow changes in the forearm skin vessels to become apparent, if they are present. Therefore, if the skin vessels of the hand and forearm act alike, one would anticipate some indication of reflex arteriolar constriction in the forearm with those stimuli which do not alter the systemic circulation. For, under such circumstances, there is little likelihood that a possible constriction of skin arterioles would be exactly counteracted by a simultaneous, passive increase in the size of muscle arterioles. The possibility of an active dilatation of muscle arterioles, of course, cannot be completely ruled out. However, it seems probable that, in contrast to those of the hand, the arterioles in the skin of the forearm are little, if at all, constricted by the vasomotor system—at least insofar as we have been able to excite it.

In addition to the above differences in the reactions of the skin vessels of the hand and forearm, there also appears to be a real quantitative difference in the blood flow per unit of skin. For example, at 32° C. the average forearm flow is approximately 2 c.c. per min. per 100 c.c. of limb volume, as compared to a hand flow of 12 c.c. Even if one assumes that *all* of the resting forearm flow represents that through the skin, then the maximal flow through the skin of the forearm (13.4 per cent skin) would be 14.9 c.c. per min. per 100 c.c. of skin, whereas that through the skin of the hand (30.2 per cent skin) would be 39.7 c.c. per min. per 100 c.c. of skin. Thus, at 32° C. it is apparent that, if we disregard any muscle flow, there is almost a threefold difference in the flow of blood through the skin of the hand as compared to that of the forearm.

Anatomically, the blood vessels of the skin in these two areas differ in at least two respects. The relative number of skin capillaries and small vessels per unit of area is greater in the hand than in the forearm.[10] Possibly of equal significance are the many arteriovenous anastomoses which have been found in the palm and finger tips,[11, 12] but which, so far as we are aware, are not present in the forearm. As pointed out by Grant and Bland,[13] these arteriovenous anastomoses have an exceptionally thick muscular coat, and are capable of great variation in caliber and presumably of causing marked variation in blood flow. The quantitative differences in blood flow through the hand and forearm may be accounted for in part by the difference in vascularity of the skin in the two areas. However, the stability of

the forearm flow, in contrast to the marked spontaneous fluctuations in flow in the hand, together with the differences in response to vasomotor stimulation, can be best explained by the fact that there are no arteriovenous anastomoses in the forearm such as those which are present in portions of the skin of the hand. Grant and Pearson[1] have come to a somewhat similar conclusion.

These studies indicate, therefore, that observations on blood flow and vascular reactions in one skin area cannot necessarily be applied to others at the periphery. They also show that the arteriovenous anastomoses are under the control of the vasomotor system to a much greater degree than are the ordinary arterioles of the skin. Further, the fact that blood flow through the forearm, in contrast to that through the hand, is unaffected by stimuli which do not alter the systemic circulation and is enhanced by those which appear to increase cardiac output suggests that the resting forearm is better than the hand for the study of qualitative changes in the peripheral circulation.

SUMMARY AND CONCLUSIONS

1. The effect of pinching, mental arithmetic, and hyperventilation upon blood flow and volume of the hand and forearm of thirty subjects was studied.

2. The blood flow through the hand regularly diminished in response to all stimuli, whereas that through the forearm was either unaffected, or generally increased in those instances in which the stimulus caused a rise in blood pressure.

3. Evidence is presented to indicate that the diminution in limb volume which is caused by these stimuli is the result both of venous and arteriolar constriction in the case of the hand, and almost solely of venous constriction in the case of the forearm. The increases in volume which often occur in the forearm are largely the result of passive arteriolar dilatation.

4. It is suggested that the forearm is more satisfactory for qualitative studies of systemic peripheral blood flow, because, in contrast to the hand, the arterioles of this portion of the limb appear to be relatively free from vasoconstrictor impulses.

5. It is suggested that the forearm is also satisfactory for the study of venous responses.

6. The qualitative differences in vasomotor response in the hand and forearm may be caused, in part, by the fact that arteriovenous anastomoses are present in the skin of the palm and finger tips, and absent in the skin of the forearm.

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THE EFFECT OF CERTAIN DRUGS ON THE CORONARY BLOOD FLOW OF THE TRAINED DOG

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THE various methods available for studying coronary blood flow have been discussed by Wiggers.[1] With one exception, all of the methods require general anesthesia, artificial respiration, and certain procedures such as inserting cannulas into the heart or its vessels. Any one of these factors might conceivably result in alterations in the normal functions of the heart. In experiments with isolated, perfused hearts, or the heart-lung preparation, the peripheral vascular effects of a drug and the possible cardiovascular reflexes elicited by the drug are eliminated. The importance of such mechanisms is obvious if a study of the total effect of the drug in question is the object of the experiment. Even when observations are made on the whole animal, as is possible with a number of methods, general anesthesia and artificial respiration are usual accompaniments. The only method thus far available that permits continuous observations on coronary blood flow in the absence of complicating factors such as those just mentioned is the thermostromuhr. By its use, the effect of drugs and other stimuli may be observed on animals in virtually a normal state which closely simulates the conditions under which the drugs are used in medical practice.[2, 3]

Although, by the use of other methods, numerous and valuable investigations have been made of the effects of certain drugs on the coronary flow, it seemed worth while to ascertain, by means of the thermostromuhr, the effect of these drugs on the coronary blood flow of the trained dog. Therefore, we are reporting two series of experiments in which the action of a number of drugs on the flow in the right and in the circumflex branch of the left coronary artery has been observed. The drugs chosen are in more or less common use by cardiologists and internists.

The influence of digitalis,[4] the glucosides of digitalis,[5] epinephrine, nitroglycerin, amyl nitrite, and thyroxine[2] on the coronary blood flow of the trained dog has been reported previously.

METHODS

Following a period of training which had accustomed the dogs to lie quietly on the laboratory table, the thermostromuhr units were placed on the coronary arteries with the animals under general anesthesia and with the use of sterile technique.

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In the case of the left coronary, the heart was approached through an incision at the fifth intercostal space. The pericardium was incised, and the cut edges were grasped by curved hemostats by means of which the heart could be mobilized as desired. The circumflex branch of the left coronary artery was isolated from its bed by careful dissection and freed of all adherent extraneous tissue. The unit was applied. A small cap designed to close the slit through which the artery was inserted was then fixed in place. We have found it advantageous to suture the two lateral lead wires with fine catgut to the myocardium at a point near the unit. This procedure aids in maintaining the unit in place. The pericardium was then closed by interrupted sutures, following which the chest was closed in the usual manner. Since, in the dog, thoracotomy on one side results in pneumothorax on the other, artificial insufflation must be supplied throughout the operation. The surgical procedures for applying a thermostromuhr unit to the right coronary artery were the same as for the left, except that the heart was exposed through an incision at the fourth intercostal space. After the animal had recovered from the immediate effects of the operation, which usually required from twenty-four to forty-eight hours, observations on the effects of the various drugs were begun.

The thermostromuhr method and the units used were the same as those previously described.[6, 7] The blood flow was recorded photographically, as in experiments previously reported.

RESULTS

The effect of the following drugs on the blood flow through both of the vessels was ascertained: (1) theophylline ethylenediamine (aminophylline); (2) atropine sulfate; (3) pyridine betacarbonic acid diethylamide (coramine); (4) epinephrine; (5) histamine acid phosphate; (6) muscle adenosine phosphoric acid (M.A.P.); (7) nitroglycerin; (8) papaverine; and (9) pitressin. In addition to the foregoing drugs, the influence of acetyl-beta-methylcholine chloride (mecholyl) on the flow in the left coronary was observed, and the effect of anesthesia with pentobarbital sodium (nembutal) on the flow in the right coronary artery was studied. The drugs, with one or two exceptions, were given into the saphenous vein, and the injection time was from fifteen to thirty seconds. Thus an effective concentration in the blood was assured, and the question of absorption obviated. Typical results obtained with each drug are described and the essential data on representative experiments are summarized in Tables I and II.

Theophylline Ethylenediamine (Aminophylline).—Gilbert and Fenn,[8] with doses of theophylline ethylenediamine corresponding to the average human dose, reported a vasodilator effect on the coronary arteries, as indicated by an increased return flow through the coronary sinus of the dog. Stoland, Ginsberg, Loy, and Hiebert[9] found that doses of 6 to 5 mg. per kilogram produced general vasodilatation, as well as local coronary dilatation. They reported considerable variation in the duration of the increased coronary sinus flow, which, on the average, was 21.6 minutes. Fowler, Hurevitz, and Smith[10] have reviewed the literature on the xanthine derivatives, including theophylline ethylenediamine. In their experiments they found that this drug was the most effective of a series in augmenting the coronary flow in the isolated perfused heart

TABLE I

EFFECT OF CERTAIN DRUGS ON THE BLOOD FLOW IN THE CIRCUMFLEX BRANCH OF THE LEFT CORONARY ARTERY OF THE TRAINED DOG

DOG NO., WEIGHT	DATE	DRUG* AND DOSE	BLOOD FLOW (C.C. PER MINUTE)			DURATION OF EFFECT
			CONTROL	MAXIMAL	PER CENT OF CHANGE	
1 12 kg.	9/28/38	Aminophylline 240 mg.	48	55	15	Blood flow 52 c.c. per min. after 17 min.
2 7.5 kg.	9/24/38	Aminophylline 120 mg.	46.5	73	57	2 minutes, 30 seconds
3 15 kg.	10/11/38	Aminophylline 240 mg.	40	68	70	2 minutes
2 7.5 kg.	9/26/38	Aminophylline 240 mg.	49.5	135	173	16 minutes
4 16.4 kg.	8/18/38	Atropine 2 mg.	59	110	86	49 minutes
4 17.2 kg.	8/27/38	Coramine 250 mg.	112	192	71	7 minutes
5 8.4 kg.	6/10/38	Coramine 125 mg.	39	90	131	14 minutes
5 8.4 kg.	6/10/38	Coramine 150 mg.	30	70	133	9 minutes, 30 seconds
1 12 kg.	9/30/38	Epinephrine 0.2 c.c. 1:100,000	43	55	28	
1 12 kg.	9/29/38	Epinephrine 0.2 c.c. 1:20,000	54	70	30	4 minutes
6 14.5 kg.	2/17/38	Epinephrine 0.05 c.c. 1:1000	57	97	70	3 minutes
6 14.5 kg.	2/17/38	Epinephrine 0.1 c.c. 1:1000	53	92	74	1 minute
3 15 kg.	10/10/38	Histamine 0.1 mg.	53	135	155	2 min.; 12 min. after injection, flow 47.5 c.c. per min.
1 13 kg.	10/ 3/38	Histamine 0.5 mg.	44	130	195	Flow 58 c.c. per min. after 11 min.
1 12.2 kg.	10/10/38	Histamine 0.1 mg.	54.5	185	239	3 minutes
1 13 kg.	10/ 1/38	M.A.P. 10 mg.	49	120	145	3 minutes
4 16.5 kg.	8/22/38	M.A.P. 10 mg.	60	225	275	1 minute, 30 seconds
7 13.2 kg.	8/27/38	M.A.P. 20 mg.	33.5	145	333	3 minutes
1 13 kg.	9/30/38	Mecholyl 0.2 mg.	43	84	95	3 minutes
3 15 kg.	10/11/38	Nitroglycerin 0.65 mg.	63	85	35	3 minutes
1 12 kg.	10/ 6/38	Nitroglycerin 1.3 mg. per os	45	72	60	Flow 64 c.c. per min. after 16 min.
1 13 kg.	10/ 4/38	Nitroglycerin 0.65 mg. per os	46	78	70	Flow 61 c.c. per min. after 16 min.
1 12 kg.	10/ 6/38	Nitroglycerin 0.65 mg.	54	93	72	Flow above control after 3 min.
1 13 kg.	10/ 3/38	Papaverine 15 mg.	44.5	86	93	2 minutes, 30 seconds
4 17.2 kg.	8/30/38	Pitressin 4 pressor units	125	0	−100	Flow 88 c.c. per min. after 15 min.
1 13 kg.	10/ 5/38	Pitressin 1 pressor unit	39	14	−64	Flow 36 c.c. per min. after 45 min.
1 12 kg.	9/30/38	Pitressin 2 pressor units	36.5	12	−67	

*Unless stated otherwise, the drug was given intravenously.

TABLE II

EFFECT OF INTRAVENOUS ADMINISTRATION OF CERTAIN DRUGS ON THE BLOOD FLOW IN THE RIGHT CORONARY ARTERY OF THE TRAINED DOG

DOG NO., WEIGHT	DATE	DRUG AND DOSE	BLOOD FLOW (C.C. PER MINUTE)			DURATION OF EFFECT
			CONTROL	MAXIMAL	PER CENT OF CHANGE	
1 17 kg.	12/ 2/38	Aminophylline 480 mg.	12	15.5	29	Flow above control after 24 minutes
2 19.5 kg.	1/26/39	Aminophylline 480 mg.	23	37	61	Flow above control after 16 minutes
3 12.2 kg.	1/12/39	Aminophylline 240 mg.	26	49	88	6 minutes
4 20.8 kg.	12/30/38	Aminophylline 240 mg.	20	38	90	3 minutes
4 20.8 kg.	12/30/38	Aminophylline 480 mg.	18	47	161	Flow above control after 18 minutes
3 12.2 kg.	1/13/39	Atropine 1.5 mg.	26.5	31.5	19	15 minutes
3 12.2 kg.	1/12/39	Atropine 1 mg.	22.5	27	20	Flow above control after 12 minutes
2 19.5 kg.	1/27/39	Atropine 2 mg.	30	39	30	Flow had not decreased after 18 minutes
3 12.2 kg.	1/14/39	Atropine 2 mg.	49	86	76	Flow above control after 18 minutes
4 20.8 kg.	12/30/38	Coramine 375 mg.	22	38	73	4 minutes
1 17 kg.	12/ 2/38	Epinephrine 0.05 c.c. 1:1000	14	23.5	68	1 minute, 30 seconds
4 20.8 kg.	12/29/38	Epinephrine 0.025 c.c. 1:1000	19	42	121	2 minutes
4 20.8 kg.	12/31/38	Epinephrine 0.025 c.c. 1:1000	20	48.5	142	8 minutes
1 17 kg.	12/ 2/38	Epinephrine 0.05 c.c. 1:1000	11	34	209	2 minutes, 30 seconds
2 19.5 kg.	1/26/39	Histamine 0.1 mg.	21	33	57	2 minutes
1 17 kg.	12/ 2/38	Histamine 0.125 mg.	15	27	80	2 minutes, 30 seconds
4 20.8 kg.	12/29/38	Histamine 0.2 mg.	18	36	100	2 minutes
4 20.8 kg.	12/30/38	M.A.P. 10 mg.	20	54	170	2 minutes
2 19.5 kg.	1/28/39	Nembutal 300 mg.	35	56	60	Flow 15 per cent above control 82 min. after injection
4 20.8 kg.	12/29/38	Nitroglycerin 0.86 mg.	23	30	30	1 minute, 30 seconds
2 19.5 kg.	1/26/39	Nitroglycerin 0.86 mg.	26	39	50	2 minutes
1 17 kg.	12/ 2/38	Nitroglycerin 1.3 mg.	14.5	22	52	2 minutes
4 20.8 kg.	12/29/38	Nitroglycerin 1.3 mg.	18	35	94	2 minutes
3 12.2 kg.	1/12/39	Nitroglycerin 0.86 mg.	21	42	100	1 minute
3 12.2 kg.	1/13/39	Papaverine 20 mg.	25	38	52	3 minutes
3 12.2 kg.	1/13/39	Pitressin 1 pressor unit	27	8	−70	Flow below control 13 min. after injection
4 20.8 kg.	12/29/38	Pitressin 1 pressor unit	16	5.5	−66	Flow below control 19 min. after injection
2 19.5 kg.	1/26/39	Pitressin 0.5 pressor unit	25	4.5	−82	Flow below control 13 min. after injection

of the rabbit, and, furthermore, they reported that it promoted the development of collateral circulation after cardiac infarction had been experimentally induced in the dog.

Doses of from 120 to 240 mg. produced an increase in the flow in the left coronary of from 15 to 173 per cent. With similar, and larger, doses, the flow in the right coronary increased by amounts ranging from 29 to 161 per cent. The duration of the effect was variable in both vessels. In some cases the flow had returned to the control value within two minutes, whereas, in others, the flow was greater than the control value for as long as twenty-four minutes after the injection. These results are in essential agreement with those of previous workers (Fig. 1).

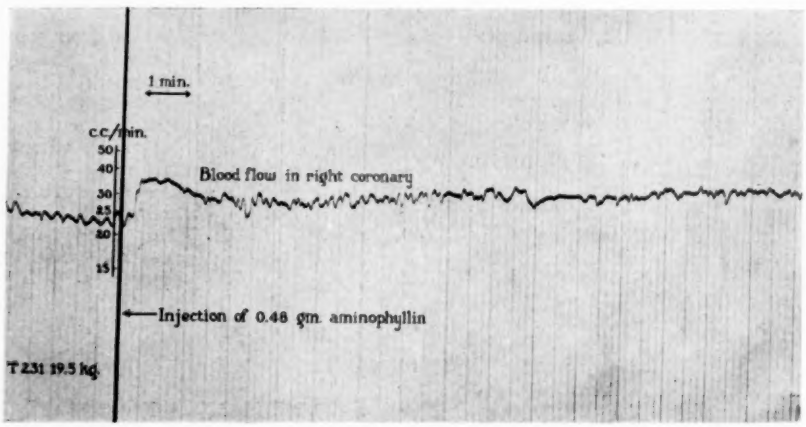

Fig. 1.—A photographic record of the blood flow in the right coronary artery of a trained dog weighing 19.5 kg. At arrow, 0.48 Gm. of theophylline ethylenediamine (aminophyllin) was injected.

Atropine Sulfate.—Although atropine is not recommended for the purpose of increasing coronary blood flow, its ability to do so has been reported by Anrep and Segall,[11] Rein,[12] Narayana,[13] and Anrep.[14] Since atropine is employed therapeutically in a variety of pulmonary and cardiac disturbances, and since it is the principal anhidrotic in common use, its possible effect on coronary flow should be more generally recognized. In sufficient doses, marked cardiac acceleration, caused by vagus paralysis, follows its administration. It was this action of the drug that caused us to include it in the present series. In one experiment an intravenous injection of 2 mg. of atropine sulfate increased the flow in the left coronary artery by as much as 86 per cent, and the flow was 25 per cent above the control level at the end of forty-nine minutes. Four experiments were done on the blood flow in the right coronary artery. The dose was from 1 to 2 mg. given intravenously; the increase in flow ranged from 19 to 76 per cent. The duration of the effect was from twelve to eighteen minutes, or longer. In agreement with previous investigators, who had used anesthetized animals, we found that the coronary blood flow in the trained dog was significantly augmented by

the doses of atropine used. An increased pulse rate was an invariable accompaniment of the increased coronary flow (Fig. 2).

Pyridine Betacarbonic Acid Diethylamide (Coramine).—Greene[15] reported prompt and pronounced coronary dilatation, resulting in an increase of 60 per cent in coronary sinus outflow, with a decrease in blood pressure of 16 per cent, as a result of the administration of coramine. Stoland and Ginsberg[16] have reviewed the literature on coramine and have reported their results with this drug on the denervated heart-lung preparation and the intact animal under ether anesthesia. They measured the coronary outflow by means of a modified Morawitz-Zahn cannula and observed a marked increase (from 70 to 80 per cent) in coronary sinus flow in both preparations. They concluded that coramine in small doses is a general vascular dilator, but in large doses is more effective as a coronary dilator.

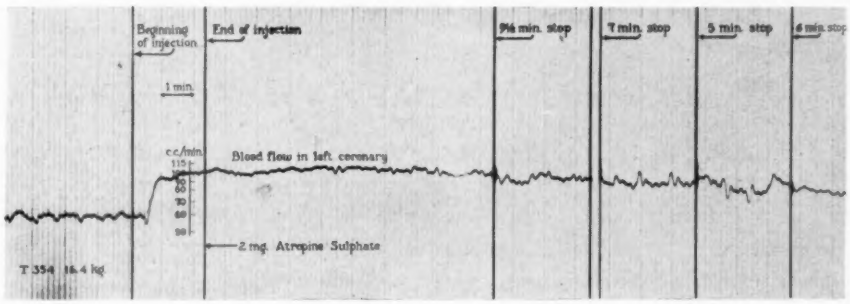

Fig. 2.—A photographic record of the blood flow in a trained dog, showing the response of the flow in the circumflex branch of the left coronary artery to 2 mg. of atropine sulfate. Weight of dog, 16.4 kg.

The results of our observations on the effect of coramine on the coronary flow of the trained dog are qualitatively the same as those of previous workers who used other methods. Doses varying from 125 to 250 mg. of this drug caused an increase of 71 to 133 per cent in the blood flow through the left coronary artery. The duration of the effect was from seven to fourteen minutes. A dose of 375 mg. caused a 73 per cent increase in the flow in the right coronary artery, but recovery from the effect of the drug was complete in four minutes.

Epinephrine.—That epinephrine in proper doses increases coronary blood flow is well established, but the mechanism by which this result is accomplished is still uncertain.[17] Such a question cannot be answered by experiments on the trained dog. To ascertain whether a similar increase occurs in both the right and left coronary arteries was the purpose of further observations on epinephrine, since Rein observed only an 8.1 per cent increase in right coronary blood flow after giving epinephrine to a dog with intact vagi. In a series of experiments on the effect of epinephrine on the flow in the right coronary artery, from 0.025 to 0.05 c.c. of a 1:1,000 solution caused increases in flow of from

68 to 209 per cent. The duration of the effect was from one to eight minutes. In addition to the data just recorded, another series of observations was made on the effect of smaller doses of epinephrine on the flow in the left coronary artery. Doses varying from 0.2 c.c. of a 1:100,000 solution to 0.1 c.c. of a 1:1,000 solution caused an increase in flow of from 28 to 74 per cent in the left coronary artery. In five of the eight observations on the two coronaries, the duration of the effect was three minutes, or less. It may be seen from these and previous data that epinephrine causes a similar augmentation of blood flow in both the right and left coronary arteries of the trained dog.

Histamine Acid Phosphate.—Gunn[18] has reported that this drug causes acceleration and augmentation of the beats of the isolated perfused hearts of rabbits and cats, with diminution of the coronary outflow in the heart of the rabbit, but increased outflow from the coronaries of the cat. Anrep, working with human heart-lung preparations, found that coronary vasodilatation occurred following injections of histamine. This amine increases the coronary blood flow of the heart-lung preparation of the dog, according to the observations of Narayana. We were stimulated to determine whether there would be a similar effect in the trained dog. In the presence of the marked peripheral dilator effects that histamine is known to produce in the dog, would it be as capable of increasing coronary blood flow as such drugs as nitroglycerin and amyl nitrite? This question was answered in the affirmative, as the following experiments attest. In a series of observations on the right and left coronary arteries, histamine caused an increase in flow as great as that which was produced by the majority of the drugs used in our experiments. Doses of from 0.1 to 0.5 mg. of this drug caused increases of flow varying from 155 to 239 per cent in the left coronary artery. The major effect was usually dissipated within three minutes following the injection. In one instance the volume flow fell below the control level, where it remained for twelve minutes, whereas in another instance the flow continued to be increased for eleven minutes. Doses of from 0.1 to 0.2 mg. of histamine caused increases of from 57 to 100 per cent in the right coronary flow. The complete effect was of short duration, lasting, at most, only two minutes and thirty seconds.

Muscle Adenosine Phosphoric Acid (M.A.P.).—Wedd[19] has recently reported observations on the dilating effect of adenosine, adenylic acid (yeast and muscle), adenine, and guanosine on the isolated perfused heart of the rabbit. It was found that all of these preparations dilated the coronary arteries. According to Wedd, adenosine is about twenty times as powerful a dilator as sodium nitrite. The dilator effect of adenosine was independent of change in heart rate and of the action of the drug on the cardiac muscle.

Greene has reviewed the literature on certain organic extracts and drugs. Included were such preparations as the cardiac hormone of

Frey (padutin), pancreatic extract, and muscle extract. All of these preparations caused a fall in blood pressure, with varying increases in coronary blood flow. When the fall in blood pressure was prevented, the coronary flow was increased.

In the trained dog, muscle adenosine phosphoric acid produces a marked, but transient, augmentation in coronary blood flow. A dose of 10 mg. caused an increase of 170 per cent in the flow in the right coronary artery. Doses of from 10 to 20 mg. augmented the left coronary flow by as much as from 145 to 333 per cent. In both vessels the duration of the effect was short; the flow had returned to the control value within three minutes (Fig. 3).

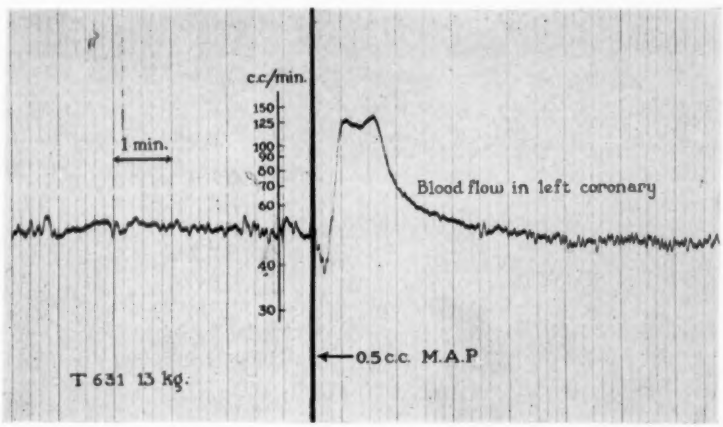

Fig. 3.—A photographic record of the blood flow in the circumflex branch of the left coronary artery of a trained dog in response to 0.5 c.c. (10 mg.) of muscle adenosine phosphoric acid. Weight of dog, 13 kg.

Acetyl-beta-methylcholine chloride (Mecholyl).—Narayana reported that in the heart-lung preparation of the dog the injection of 6 mg. of acetylcholine caused an increase in coronary sinus flow, with no change in heart rate. Weinstein, Jochim, and Bohning[20] observed an increase in coronary perfusion flow following injections of acetylcholine and beta-methylcholine into isolated, fibrillating hearts. Anrep reported an increased flow in heart-lung preparations and in the whole animal. The same increase occurs when injections of acetyl-beta-methylcholine chloride are given to the trained dog. As Anrep stated, this effect on coronary flow is different from what would have been suspected. At least on theoretic grounds, it might be supposed that drugs which have an action on the cardiovascular system similar to vagal stimulation might reduce the coronary blood flow, but in one experiment an injection of 0.2 mg. of acetyl-beta-methylcholine chloride caused an increase in the left coronary flow of 95 per cent.

Nitroglycerin.—Doses of from 0.65 to 1.3 mg. of this drug caused increases in flow in both coronary arteries. The augmentation in the right coronary varied from 30 to 100 per cent, and that in the left from

35 to 72 per cent. The effect lasted from one to three minutes. In two experiments, similar doses given by mouth produced increases in flow of as much as 70 per cent, and the flow was above the control level after sixteen minutes.

Pentobarbital Sodium (Nembutal).—Because of the known vasodilator action of the barbiturates, it might be inferred that general anesthesia produced by these agents should result in an increased coronary blood flow. This appears to be true. In one experiment an intravenous injection of 300 mg. of pentobarbital sodium produced a maximal increase of 60 per cent in the blood flow in the right coronary. The flow was 15 per cent above the control level at the end of eighty-two minutes.

Papaverine.—This drug increased both the right and the left coronary flow by 52 and 93 per cent, respectively, when given in doses of 20 and 15 mg. The duration of the effect was about three minutes. This result is in agreement with the observations of Anrep on the human heart-lung preparation.

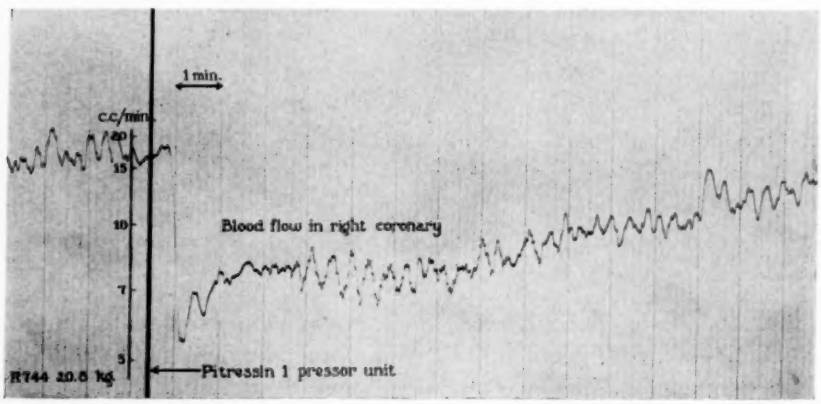

Fig. 4.—A photographic record of the blood flow in the right coronary artery of a trained dog. At arrow, 1 pressor unit of pitressin was given intravenously. Weight of dog, 20.8 kg.

Pressor Principle of the Posterior Pituitary (Pitressin).—Anrep and Stacey,[21] who studied the sinus outflow by means of the hot-wire anemometer, found that pituitary extract (B. D. H.) caused a 75 per cent decrease in coronary blood flow. Gruber and Kountz[22] reviewed the literature on pituitary extracts in relation to the coronary arteries and reported experiments on the isolated perfused heart of the rabbit in which they found that pitressin produced vasoconstriction. Narayana reported that 2 units of pituitrin decreased the coronary sinus outflow in the heart-lung preparation of the dog; this was attended with an insignificant change in pulse rate. This result has been a surprise to many because of the fact that the blood pressure frequently rises following injections of pitressin. The degree of decrease in coronary flow is similar

to that which occurs in other vessels, as reported by Geiling, Herrick, and Essex,[23] who found a striking decrease in the blood flow in the femoral and carotid arteries of the trained dog. Since posterior pituitary preparations are widely used in obstetrics and roentgenology, their action in reducing coronary flow, as well as the circulation in other vessels, should be stressed. Profound decreases in right and left coronary blood flow were observed immediately after the intravenous injection of from 0.5 to 2 pressor units. The decrease in the flow in these vessels was from 64 to 82 per cent. The maximal decrease was of short duration, but the flow remained below the control level for as long as forty-five minutes (Fig. 4).

COMMENT

The data obtained on the coronary blood flow of the trained dog are of necessity synthetic. As pointed out by Katz, Jochim, and Bohning,[24] the values obtained with the thermostromuhr depict the coronary flow as a resultant of all of the controlling factors involved, but the evaluation of each individual factor is a matter of deductive reasoning. The effect of the various drugs on the general circulation can only be inferred from other studies. It would have been desirable to obtain, with each drug, simultaneous records of the flow in both coronary vessels and the systemic arterial blood pressure. However, such extensive procedures were considered excessive for the trained dog, but highly feasible with animals under a general anesthetic. In a subsequent report, data on a series of experiments of this nature will be presented, and the simultaneous effect on the general circulation of the drugs used will be discussed.

SUMMARY AND CONCLUSIONS

Changes in the blood flow in the right and left coronary arteries of the trained dog were qualitatively the same in response to the drugs given.

Drugs that are known to lower blood pressure, such as theophylline ethylenediamine (aminophylline), histamine, muscle adenosine phosphoric acid, acetyl-beta-methylcholine chloride (mecholyl), nitroglycerin, and papaverine, when administered in appropriate doses, markedly increased the coronary flow. The increase in flow with certain of these drugs was as great as 200 to 300 per cent. The augmentation of flow was accompanied by an acceleration of the heart rate. Pyridine beta-carbonic acid diethylamide (coramine), which may raise the blood pressure under certain conditions, caused an increase in coronary flow similar to that produced by the drugs just named. With two possible exceptions, the action of all of the foregoing drugs was of short duration when given intravenously.

Anesthesia with pentobarbital sodium (nembutal), in one experiment, caused a prolonged increase in coronary blood flow, with a maximal increase of 60 per cent.

Among the drugs that usually raise blood pressure, pitressin decreased the coronary blood flow as much as 80 per cent and lowered the heart rate, which is similar to its effect on the flow in other vessels which have been previously studied.

Atropine augmented the coronary flow by as much as 86 per cent and increased the heart rate, but it had little effect on the blood pressure in control experiments.

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STUDIES ON MERCURIAL DIURESIS

III. The Alteration Induced in the Cerebrospinal Fluid Pressure

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ATTENTION has been directed to the elevation of the cerebrospinal fluid pressure in patients suffering from congestive heart failure. A similar increase in cerebrospinal fluid pressure has been observed in cases of mediastinal tumor and tuberculous mediastinitis, as well as after deep jugular vein ligation. Weed and Hughson[1] have demonstrated by means of animal experiments that an alteration in intracranial pressure results in a change in pressure in the cerebrospinal fluid in the same direction, but of less magnitude. An elevation of pressure in the intracranial veins immediately produces a rise in the pressure of the cerebrospinal fluid. In the Queckenstedt maneuver, compression of the jugular veins is followed by a sudden increase in cerebrospinal pressure. This drops rapidly to its previous level as the jugular pressure is discontinued. The rise is obviously caused by an abrupt and transitory engorgement of the intracranial tributaries of these veins.

Therefore, the elevation in the pressure of the cerebrospinal fluid in cases of congestive heart failure can be explained mainly as a result of the rise in venous blood pressure which accompanies the venous engorgement caused by insufficiency of the right side of the heart. This increased venous blood pressure is transmitted to the intracranial and intraspinal veins. Edema of the brain is a factor contributing to the increased intracranial pressure. According to Fishberg, the amount of spinal fluid is not increased.

Both the venous blood pressure and the spinal fluid pressure are elevated in cases of cardiac failure, the latter more than the former. Improvement produces parallel changes (decrease) in these pressures, although there is a slight lag in the fall of the cerebrospinal fluid pressure. In a previous communication[2] we demonstrated the effect of mercurial diuresis on the venous blood pressure. The inference naturally was that mercurial diuresis would profoundly influence the elevated cerebrospinal fluid pressure in cases of right-sided heart failure.

METHOD OF STUDY

Spinal fluid pressure measurements were made by means of lumbar puncture, using the direct manometric technique, with the patient in the left lateral position; novocain was the anesthetic. The measure-

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ments were made just prior to the intravenous injection of the mercurial diuretic, and again twenty-four hours subsequently. Direct venous blood pressure estimations were recorded at approximately the same time. The latter were made with the patient in the supine position, employing the technique described in the communication already referred to. The drug used was Esidrone (Ciba), a new mercurial diuretic which is particularly effective. The dosage was indicated on the chart. All injections were given intravenously.

Our experience, as well as that of other investigators, has indicated that there is a direct relationship between venous blood pressure and spinal fluid pressure. We have previously demonstrated the constancy of the venous blood pressure in cases of heart disease in which improvement does not occur. The spinal fluid pressure, likewise, is fairly constant, varying directly with the venous pressure. In the following experiment the measurements were made almost simultaneously on three successive days, at twenty-four-hour intervals; the patient received no treatment except bed rest.

TABLE I

W. L.	PRESSURE IN MILLIMETERS OF WATER	
	VENOUS BLOOD PRESSURE MM.	SPINAL FLUID PRESSURE MM.
10/26	208	278
10/27	230	284
10/28	262	292

It is to be noted that the maximal variation in spinal fluid pressure was 14 mm., and that it increased in proportion to the rise of venous pressure. Symptomatically, the patient's condition became increasingly serious.

The influence of the increased intracranial venous pressure produced by the Queckenstedt maneuver is illustrated by the experiments here described. In the tables, the effect of withdrawal of small amounts of spinal fluid on the subarachnoid tension is shown. The results in seven cases of right-sided heart failure are tabulated.

TABLE II

	SPINAL PRESSURE MM.	C.C. REMOVED	SPINAL PRESSURE MM.	DECREASE MM.
A. L.	330	15	270	60
S. J.	160	10	60	100
J. M.	200	15	60	140
O. M.	200	15	170	30
S. N.	320	15	170	150
J. M.	200	8	160	40
D. A.	250	15	200	50

In Table III the Queckenstedt test was done prior to, and subsequent to, the removal of the indicated volume of spinal fluid.

TABLE III

	SPINAL PRESSURE MM.	QUECKENSTEDT MM.	C.C. REMOVED	SP. PRESS. MM.	QUECK. MM.
J. G.	190	300	7	160	270
W. T.	250	300	5	220	260
W. S.	100	110	10	85	95
A. F.	340	420	15	160	220
J. C.	200	240	10	150	200
T. C.	150	180	10	130	140

These observations demonstrate that pressure on the jugular veins increases the spinal fluid pressure, that the withdrawal of fluid decreases the spinal fluid pressure, and that the Queckenstedt procedure after the removal of fluid does not elevate the spinal pressure to the previous Queckenstedt level. It can be deduced from this observation that, under these conditions, changes in the volume of the spinal fluid, in addition to the level of intracranial venous blood pressure, affect the spinal fluid pressure. W. G. Harrison[3] reports immediate improvement in cases of heart failure following spinal drainage. This suggests therapeutic application of the procedure. Table IV shows the pronounced alterations in spinal fluid and venous pressures which occurred after intravenous administration of the mercurial diuretic. The following types of heart disease, attended with right-sided heart failure, were included in this study: rheumatic, syphilitic, hypertensive, coronary arteriosclerotic, and chronic cor pulmonale. The urinary output for the twenty-four hours preceding the injection, and the twenty-four hours subsequent to the injection, is indicated. The venous pressure measurements, with the decrease produced by the diuresis, are shown. Similarly, the simultaneous spinal fluid pressure measurements, with the resulting diminutions, are clearly demonstrated.

COMMENT

The maximal decrease in intrathecal pressure following withdrawal of 15 c.c. of spinal fluid was 150 mm., whereas the greatest fall which resulted from mercurial diuresis was 280 mm. The average diminutions, compared similarly, were 81 mm. when fluid was withdrawn, and 133 mm. following diuresis. It is to be noted, also, that the maximal decreases in spinal fluid pressure occurred when the fall in venous pressure was most significant. In the studies on venous blood pressures to which we have already referred, the relation of diuresis to the venous pressure was demonstrated. The maximum decline of the latter occurs with more pronounced diuresis. The results in Table IV indicate that there is a similar relationship to the decline of spinal fluid pressure. For example, T. M. had a diuresis amounting to 5700 c.c., with a resulting decrease of 198 mm. in venous pressure, and a fall of 280 mm. in intrathecal pressure. Thus, a direct relationship between urinary out-

TABLE IV

NAME	DOSE	DATE	24-HOUR URINARY OUTPUT (C.C.)	INCREASE (C.C.)	VENOUS PRESSURE (MM.)	DECREASE (MM.)	SPINAL FLUID PRESSURE (MM.)	DECREASE (MM.)
J. S.	Esidrone, 1 c.c.	5/16	1300		244		315	
		5/17	4500	3200	150	94	118	197
W. S.	Esidrone, 1 c.c.	5/25	1000		274		370	
		5/26	3300	2300	216	58	270	100
T. D.	Esidrone, 1 c.c.	5/27	1400		240		350	
		5/28	2500	1100	110	130	174	176
J. T.	Esidrone, 1 c.c.	6/5	400		232		286	
		6/6	1000	600	170	62	230	56
C. A.	Esidrone, 1 c.c.	6/5	800		248		340	
		6/6	4000	3200	164	84	104	236
F. C.	Esidrone, 1 c.c.	6/11	500		84		120	
		6/12	2000	1500	64	20	80	40
F. K.	Esidrone, 1 c.c.	7/27	300		216		330	
		7/28	2200	1900	136	80	230	100
H. D.	Esidrone, 2 c.c.	8/2	400		234		292	
		8/3	4600	4200	186	48	92	200
T. M.	Esidrone, 2 c.c.	7/30	600		340		480	
		7/31	5700	5100	142	198	200	280
P. A	Esidrone, 2 c.c.	8/10	800		320		350	
		8/11	3000	2200	208	112	250	100
W. T.	Esidrone, 2 c.c.	10/3	150		310		340	
		10/4	2000	1850	234	76	250	90
W. L.	Esidrone, 2 c.c.	10/28	600		262		292	
		10/29	6000	5400	132	130	150	142
W. T.	Esidrone, 2 c.c.	10/30	700		340		340	
		10/31	5000	4300	224	116	216	124
W. L.	Esidrone, 2 c.c.	11/23	400		354		340	
		11/24	3500	3100	174	180	208	132
F. L.	Esidrone, 2 c.c.	11/29	200		315		372	
		11/30	3000	2800	168	147	236	136
C. J.	Esidrone, 2 c.c.	12/8	400		112		160	
		12/9	2000	1600	96	16	128	32
W. L.	Esidrone, 2 c.c.	12/8	400		352		392	
		12/9	3000	2600	208	144	276	116

put and venous and subarachnoid pressures is demonstrated. The greater the diuresis, the more pronounced is the diminution in these two pressures. Other factors probably play a part, especially the degree or elevation of the pressures before diuresis is initiated. From higher levels, a more pronounced decline can be expected. A constant mathematical ratio cannot be expressed, however, for venous pressure, spinal pressure, and urinary output.

DISCUSSION

Symptomatic improvement, especially relief of dyspnea, in congestive heart failure has been reported following spinal drainage. One might infer that lumbar puncture can be advised as a therapeutic measure.

With such an elevation of subarachnoid pressure, spinal puncture may prove dangerous. In the experience of one of us (I. F. V.), death ensued in a case in which lumbar puncture was employed to relieve dyspnea.

The tabulation demonstrates that mercurial diuresis is much more efficient in producing a decline of spinal fluid pressure than the withdrawal of spinal fluid. An elevation in venous pressure is very definitely a factor in the dyspnea of right-sided heart failure. Elevation of venous pressure is directly related to elevation of spinal fluid pressure. If intrathecal pressure is an important factor in the production of dyspnea, certainly the reduction of this pressure, by whatever means, should result in improvement. Mercurial diuresis effects this reduction, as the tabulation vividly demonstrates. The reduction is apparently the result of the effect on venous blood pressure.

SUMMARY AND CONCLUSIONS

1. Both venous blood pressure and cerebrospinal fluid pressure are elevated in cases of congestive heart failure.

2. Both pressures are fairly constant in the untreated patient when improvement does not occur. Aggravation of symptoms is usually associated with an increase in both pressures.

3. Withdrawal of spinal fluid in a case of right-sided heart failure decreases spinal fluid pressure.

4. Dyspnea is often relieved immediately after the removal of fluid causes a decrease in the spinal fluid pressure.

5. Mercurial diuresis produces a diminution in subarachnoid and venous blood pressures.

6. The decrease in cerebrospinal fluid pressure and venous blood pressure is directly related to the urinary output; the greater the mercurial diuresis, the more pronounced the fall in both pressures.

7. The fall in spinal fluid pressure which follows mercurial diuresis is much greater, on the average, than that produced by spinal drainage, and is not accompanied by the possibility of danger.

8. Venous blood pressure and spinal fluid pressure decrease as improvement occurs.

9. Decreases in both venous pressure and cerebrospinal pressure are objective evidences of improvement in cases of congestive heart failure.

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A STUDY OF PRECORDIAL LEADS IN SUBJECTS WITH CONGENITAL DEXTROCARDIA AND SITUS INVERSUS VISCERUM

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DURING the course of electrocardiographic observations on an adult with congenital dextrocardia and situs inversus viscerum, we became interested in the precordial leads in subjects with this anomaly. A search of the literature failed to reveal more than two instances in which precordial leads had been taken on subjects with congenital dextrocardia. Edwards and Vander Veer,[1] in a study of chest leads, reported these leads on one such normal subject. Manchester and White[2] reported a single precordial lead on such a patient. In the latter instance, however, there were the complications of hypertension and coronary heart disease.

Theoretically, the precordial leads of a subject with congenital dextrocardia and situs inversus viscerum should not differ materially from those of a person whose heart is on the left side. This should be true provided the application of the "exploring" electrode is corrected for the dextro-position of the heart. In order to throw light upon this subject, and because of the scarcity of reports on precordial leads in cases of congenital dextrocardia with situs inversus viscerum, we were prompted to report observations on seven such subjects.

METHODS

Six of our subjects showed no clinical evidence of heart disease; a seventh, although likewise free from clinical manifestations of heart disease, had a systolic hypertension; her blood pressure was 180/90. The presence of dextrocardia with situs inversus viscerum was demonstrated roentgenologically in each patient. In addition to the three standard leads, precordial leads CF_1, CF_2, CF_3, CF_4, CF_5, and CF_6 were taken on each subject in the manner prescribed by the American Heart Association and the Cardiac Society of Great Britain and Ireland,[3] except that in the case of subject No. 3 the arm electrode was used as the "exploring" electrode, and the foot electrode as the "indifferent" one. The positions of the "exploring" electrode were modified, as follows: CF_1, just left of the sternal margin in the fourth intercostal space; CF_2, just right of the sternal margin in the fourth intercostal space; CF_3, on a line midway between the right sternal margin and right midclavicular line; CF_4, right midclavicular line; CF_5, right anterior axillary line; CF_6, right midaxillary line. In Leads CF_3 to CF_6, inclusive, the electrode was on a line drawn from the right sternal margin in the fourth intercostal space to the outer

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border of the apex beat, and continued around the right side of the chest at the level of the apex beat. The "indifferent" electrode was placed on the right leg. The various complexes were identified and measured according to the conventional criteria.[4] The precordial leads of subject No. 3 were analyzed as if the tracings were a mirror image, in order to correct for the position of the electrodes.

RESULTS

The results are summarized in Table I, Table II, and Fig. 1. The precordial leads in cases of congenital dextrocardia with situs inversus were found to be essentially the same as those of a normal subject with the heart on the left side. This was true provided the application of the "exploring" electrode was corrected for the dextro-position of the heart.

TABLE I

THE MEAN VALUES OF THE CHEST LEADS ON THE SIX "NORMAL" SUBJECTS

LEADS	P WAVE		P-R	QRS	Q	R	S	S-T		T	
	DUR.	AMP.	INTERVAL	DUR.	AMP.	AMP.	AMP.	SHIFT	DUR.	DUR.	AMP.
CF_1	.059	+1.19 −0.501	.136	.084	0	7.963	21.78	1.16	.249	.104	+2.730 −0.333
CF_2	.045	+1.1 −1.065	.126	.084	0	8.391	22.10	1.032	.253	.126	+2.18
CF_3	.044	+0.866 −0.750	.124	.079	0	8.435	12.026	.511	.255	.149	+2.94
CF_4	.052	+0.876 −0.916	.119	.075	0	9.168	18.13	.443	.254	.151	+2.71
CF_5	.057	+0.960 −0.687	.135	.073	.355	11.34	7.11	.221	.258	.141	+3.17
CF_6	.066	+0.866 −0.666	.134	.071	.841	7.326	3.16	.110	.247	.131	+1.89

TABLE II

THE VALUES OF THE CHEST LEADS ON SUBJECT NO. 7, WHOSE DEXTROCARDIA AND SITUS INVERSUS VISCERUM WERE COMPLICATED BY A SYSTOLIC HYPERTENSION

LEADS	P WAVE		P-R	QRS	Q	R	S	S-T		T	
	DUR.	AMP.	INTERVAL	DUR.	AMP.	AMP.	AMP.	SHIFT	DUR.	DUR.	AMP.
CF_1	.06	−1.80	.10	.078	0	5.55	25.8	+1.38	.25	.085	−0.75
CF_2	.075	−2.80	.11	.080	0	6.08	28.5		.245	.088	−1.13
CF_3	.058	−1.88	.105	.080	0	6.13	26.1	+1.0	.240	.080	−1.0
CF_4	.068	−1.70	.115	.070	0	5.50	21.8	0	.248	.078	−1.0
CF_5	.050	−1.0	.108	.073	0	10.0	1.25	0	.245	.113	−1.0
CF_6	.060	−0.875	.123	.055	0	8.25	0	.625	.240	.088	−0.725

P Wave.—In four of the six "normal" subjects the P wave was either negative or diphasic, whereas in the other two it was positive. The maximum amplitude in the six precordial leads was −1.9 mm., and the mean amplitude was about 1.0 mm. in the positive deflections and 0.8 mm. in the negative. The average duration was 0.054 sec., with maximum and minimum values of 0.085 and 0.023 sec., respectively. In general, as the "exploring" electrode was moved from the sternum toward the axilla the amplitude of the P wave decreased, and the wave tended to become hidden in the isoelectric line.

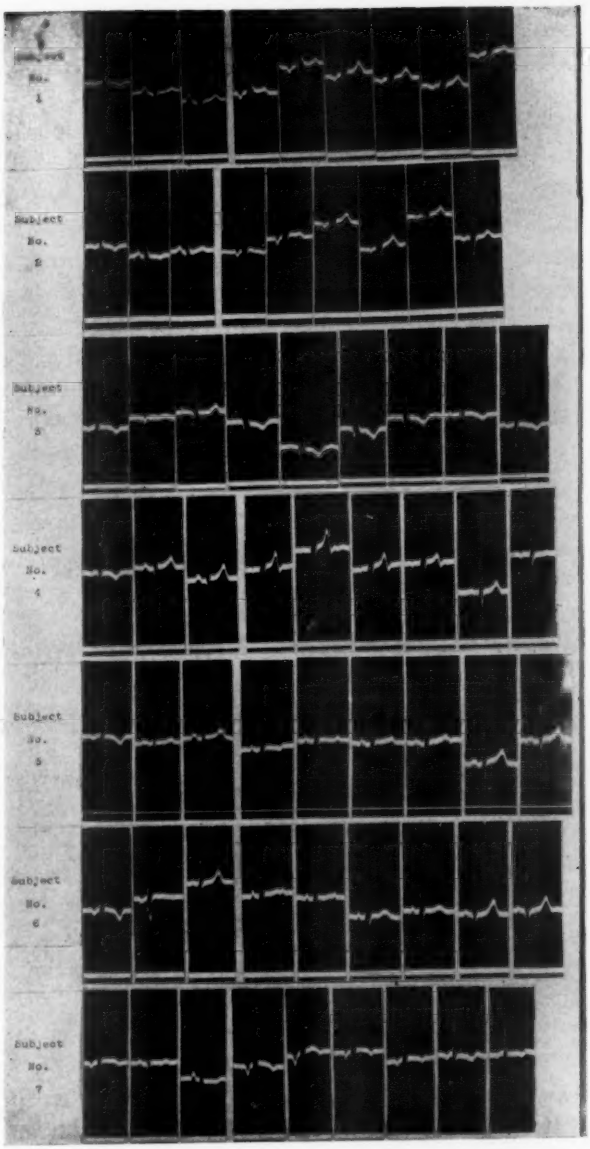

Fig. 1.—The three standard and six precordial leads in the seven subjects studied. From left to right the leads are as follows: standard Leads I, II, and III, and precordial Leads CF_1, CF_2, CF_3, CF_4, CF_5, and CF_6. See text for methods employed in taking the chest leads.

Subject No. 1, white male, aged 39 years.
Subject No. 2, white male, aged 25 years.
Subject No. 3, white female, aged 56 years.
Subject No. 4, colored male, aged 22 years.
Subject No. 5, colored female, aged 14 years.
Subject No. 6, white female, aged 33 years.
Subject No. 7, white female, aged 64 years.

P-R Interval.—The mean duration of the P-R interval was 0.112 sec., with respective maximum and minimum values of 0.163 and 0.09.

QRS Complex.—The mean duration of the QRS complex was 0.076 sec., with maximum and minimum values of 0.11 and 0.055, respectively. There was very little variation in the duration of the complex in the various precordial leads of a given subject.

Q Wave.—This wave was present in only leads CF_5 and CF_6 of three of the six subjects. No other leads showed any discernible Q wave. When present, the wave was small in all instances; the largest had an amplitude of 2.4 mm.

R Wave.—The R wave was present and greater than 2 mm. in all leads. The wave increased in amplitude as the "exploring" electrode was moved from the sternum toward the axilla, being greatest in the leads obtained from the region of the apex beat. The maximum R deflection was found to be 17.5 mm., with a mean of 8.8 mm.

S Wave.—The S wave was found to be of greatest amplitude in the lead taken from the region of the sternum. The complex decreased in amplitude as the "exploring" electrode was moved toward the axilla. The maximum S deflection was found to be 39.0 mm., with a mean of 14.1 mm.

S-T Interval.—This interval did not deviate more than 0.6 mm. from the isoelectric line in any of the leads. It was isoelectric in most instances. The interval was shifted very slightly below the isoelectric line in lead CF_5 in one case (No. 7). In a few instances the interval was shifted very slightly above the isoelectric line. The mean duration of this interval was 0.25 sec., the maximum, 0.293 sec. The duration of the interval did not vary to any marked degree from lead to lead.

T Wave.—In general, the T wave was positive in all leads. However, in CF_1 the T wave was diphasic in two subjects, isoelectric in one, and positive in the other three. In one subject the T wave was diphasic in CF_{1-4}, and positive in CF_5 and CF_6. The mean amplitude of the T wave, when it was positive, was 2.6 mm.; when negative, 0.33 mm. The maximum T deflection in any precordial lead was +4.75 mm.

The precordial leads of subject No. 7, who had systolic hypertension (180 mm. Hg), were essentially the same as those of the six subjects without any cardiovascular disease, except that the T wave was inverted in all leads except CF_5 and CF_6. In the latter two leads the wave was diphasic (Table II and Fig. 1). Although this patient showed no clinical evidence of heart disease, she was considered separately because of the systolic hypertension and inverted T waves.

COMMENT

Despite the fact that the results obtained were predictable, they do aid in establishing a definite conception of the chest leads in cases of congenital dextrocardia. Such a conception might prove to be of value

in interpreting an electrocardiogram, e.g., in a patient with dextrocardia who was suspected of having coronary occlusion. Study of a larger series of such subjects, with and without heart disease, will be necessary before there can be any generalizations.

Subject No. 7, with the systolic hypertension, although she showed no clinical evidence of heart disease, had inverted T waves in four precordial leads, which might be an indication of myocardial disease. Although it is a general rule that the T wave of the chest leads is positive in subjects without heart disease, this is not necessarily true. Sodeman[5] found that the T wave was negative in a patient with a normal heart. Subject No. 4 had diphasic T waves in all precordial leads except CF_5 and CF_6. He also showed no clinical evidence of heart disease. The correct interpretation of the T waves in these two individuals cannot be offered at this time. Further observation might disclose evidence of myocardial disease.

SUMMARY

The chest leads of seven persons with congenital dextrocardia and situs inversus viscerum were studied. None of the seven showed any clinical evidence of heart disease. One subject, however, because she had systolic hypertension, was believed to be potentially abnormal, and was considered separately from the other six. The standard leads of this one subject were normal, but she had inverted T waves in CF_{1-4} and diphasic T waves in CF_5 and CF_6. The data indicate that the chest leads of a person with congenital dextrocardia and situs inversus are approximately identical with those of an individual whose heart is on the left side, provided the technique of making the leads is altered to conform to the dextro-position of the heart.

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CLINICAL COMPARISON OF THE CRYSTALLINE GLUCOSIDES OF DIGITALIS LANATA (DIGILANID) AND THE POWDERED LEAF OF DIGITALIS

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INTRODUCTION

THREE pure crystalline glucosides have been isolated from digitalis lanata by Stoll and Kreis,[1] and are available, under the name of digilanid, as a mixture of constant proportions. This proportion is often found in the leaf. Stoll has shown[2] that the well-known glucosides, digitoxin, gitoxin, and digoxin, are degeneration products of the naturally occurring glucosides, and that those present in digilanid are different from any previously described crystalline substances. Stoll stated that the mixture of crystalline substances in digilanid has an action similar to that of digitalis lanata.

With crystalline preparations, accurate dosage, gravimetrically determined, is possible without the necessity of biologic standardization. The constant proportions of the various glucosides may well represent another advantage, and result in more uniformity from the clinical standpoint. Moe and Visscher,[3] working on the heart-lung preparation, have found that the relation between the dose effective on the myocardium and the toxic dose varies widely among the various glucosides in digilanid. Stoll has found that the proportion of the glucosides present in different samples of the leaf may vary considerably. These observations are in support of the frequently emphasized fact that different samples of leaf may differ in therapeutic effect but have similar toxic effects on animals.

The preparation has been found to be quite stable. A liquid preparation of digilanid which was opened, recorked, and kept in a bathroom medicine cabinet for about four years was compared with a fresh preparation by Vos,[4] who found no significant deterioration as determined by cat assay. This result of this severe test supports the observations of other workers.

The therapeutic efficacy of such a preparation must equal or exceed that of standard preparations before it can be accepted for use, however, in spite of any advantage of accurate dosage, uniformity, and stability which it may possess. Hochrein and Lechleitner,[5] Roth,[6] Grützmacher,[7] Nieten,[8] Rohr and Wuhrmann,[9] and others have reported clinical trials, and the present communication is concerned with the results of further clinical investigation.

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The problem was approached from three points of view: First, two patients were repeatedly digitalized with digilanid and a standard preparation of digitalis leaf;* second, a larger number were digitalized, and some of them were kept on digilanid; and third, another group was changed from a maintenance dose of digitalis leaf to a maintenance dose of digilanid. The unit dose of digitalis leaves was 0.1 Gm., which is one U.S.P. XI unit. The unit dose of digilanid was ⅓ mg. of the mixed glucosides, which was found by Rothlin[10] to equal one cat unit.

RESULTS

Controlled comparisons of digilanid and digitalis leaf.—Two patients were digitalized repeatedly in the hospital, according to a constant dosage pattern, until a definite end point had been reached in each case. Mild intoxication was produced to show any differences that might exist between the two preparations in toxic as well as therapeutic effect. The caloric, fluid, and salt intake were maintained at a constant level in order to avoid, as far as possible, irregularities in observations caused by variations in these factors. Both of these patients had been followed for several years previous to the study, and were known to have a low, but reasonably constant, cardiac reserve.

Patient A. H., Unit No. 160368, was a white woman, 44 years old, with rheumatic heart disease, mitral stenosis and insufficiency, moderate enlargement of the heart, and chronic auricular fibrillation. Functionally, she belonged in class 4; she developed symptoms and signs of cardiac insufficiency at rest in bed when she was not digitalized, but recovered, except for some persistent liver enlargement, when she became digitalized. The caloric intake was between 1780 and 1880 calories a day, except when it was reduced by nausea caused by heart failure or digitalis intoxication. The salt intake was maintained reasonably constant, usually between 3.0 and 3.5 Gm. daily. When the intake of food was reduced, the salt intake was held constant by addition of salt, except in a few instances. The fluid intake was between 1600 and 1800 c.c. daily. The only medicaments used, aside from the digitalis preparations, were barbital derivatives in fairly constant doses, and codeine in amounts of as much as .03 Gm., with or without elixir of terpin hydrate. The codeine was never given within eighteen hours before observations were to be made, for it was found to interfere.

To compare the digitalis preparations, she was given 6 units of one of them in the evening and 2 units each morning and evening thereafter, until the heart rate under basal conditions was 55 per minute. She was then given no digitalis for four weeks. On the evening of the twenty-ninth day without digitalis, one of the preparations was given again in the same way. The basal pulse rate was chosen to indicate the end point because it followed the most regular course. All of the rates at the end of the digitalization were between 53 and 56 per minute. In addition,

*Digitalis leaves (Lilly).

the arterial blood pressure and vital capacity were measured, and the patient was weighed, under basal conditions daily (with few exceptions) during digitalization and frequently during intervals between digitalizations. With equal frequency, measurements of venous pressure (direct method) and circulation time (decholin) were made during the first several months, but the latter measurement was made less often as the veins deteriorated, and both had to be discontinued after ten digitalizations because of the poor state of the veins. Many electrocardiograms and measurements of the basal metabolic rate and basal ventilation were made. A number of cardiac output measurements was made by an acetylene method before, during, and after digitalization. Fluid intake and output were measured throughout.

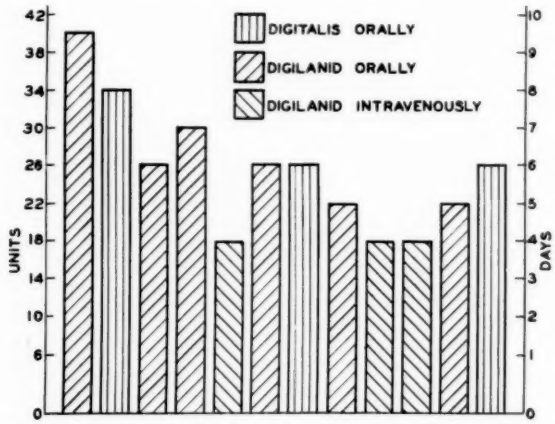

Fig. 1.—Patient A. H. Each bar indicates the digitalizing dose in units of the preparation, and the length of time over which it was administered. The units, method of administration, and criterion of digitalization are described in the text. Four weeks elapsed between the end of each period of digitalization and the beginning of the next.

The patient was digitalized according to this dosage plan twelve times; the preparation used, the dose, and the time during which it was administered are shown in Fig. 1. There was a progressive fall in requirement during the first few months. The average dose of digitalis leaf was 29 units, of digilanid orally, 28 units, and of digilanid intravenously, 18 units. Fig. 2 shows mean basal pulse rate, weight, and caloric intake curves during the period when the two preparations were being given orally. Similar curves during intravenous digitalization correspond with these. In each instance the paired curves are similar. Each administration was accompanied by nausea, and a few by a single attack of vomiting. The degree of nausea is best shown by the reduction in caloric intake, charted in Fig. 2. The low point at the beginning of the composite digitalis curve was caused by one day of low caloric intake (700 cal.), when the patient was uncomfortable because of dyspnea, cough, and palpitation. The caloric intake curve during digilanid administration falls a little earlier and begins to rise more promptly than the cor-

responding digitalis curve, but the differences are slight and probably not significant. The weight curves drop before there is any reduction in caloric intake. The weight loss was always accompanied by a slight diuresis, as indicated by the fluid balance. The other observations, including evaluation of the symptoms and signs, failed to give evidence of difference in effect between the two preparations when they were given orally.

Patient A. D., Unit No. 176930, was a white man, 41 years old, with rheumatic heart disease, marked enlargement of the heart, mitral insufficiency and stenosis, aortic insufficiency, and chronic auricular fibrillation (class 3). He did not show signs of heart failure when he was up and about the ward, although he had had failure prior to being hospitalized for this study. He took 2400 to 2500 calories, 2000 c.c. of fluid, and 5 Gm. of salt daily for several months, but some variation was allowed after it became apparent that no significant changes in weight or fluid balance were produced by digitalization.

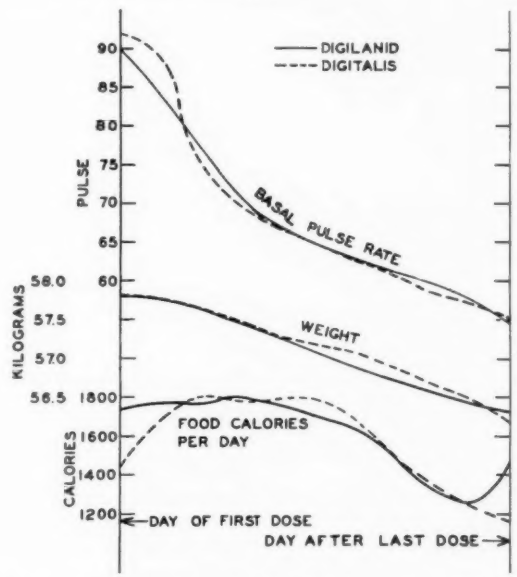

Fig. 2.—Patient A. H. Mean curves of basal pulse rate, weight, and caloric intake during digitalization with digilanid orally (six digitalizations) and digitalis leaf (three digitalizations). In constructing these mean curves the time scales of the individual curves were varied so that the horizontal lengths of the curves were equal regardless of the actual time required for digitalization.

There were several preliminary digitalizations which are not comparable because of variation in dosage or end points; the patient was then digitalized four times, at constant intervals, in the same way as patient A. H., i.e., the first dose of 6 units was given in the morning, after basal observations had been made, and 1 unit daily thereafter on successive days until the basal pulse rate reached 40 per minute. In addition to the observations made on A. H., the effect of standardized exercise was observed in the morning after the basal observations. The

exercise consisted of twelve trips over a set of Master[11] steps in one minute. The pulmonary ventilation during the exercise, and for a 3-minute period following, with the patient sitting, was measured. The volume was read every thirty seconds. Beginning fifteen seconds after the termination of the exercise, the heart rate was counted in unit periods of fifteen seconds for the remaining 2¾ minutes of the ventilation measurement.

Fig. 3 shows the dosage used in each digitalization, and the length of time over which the drug was given. The average requirement of powdered leaf was 12 units, and of digilanid, 14 units. Fig. 4 illustrates the changes in the pulse rate and vital capacity that occurred during digitalization. Because they show more individual variation than those of patient A. H., and because there are only four of each, individual rather than mean curves are given. In spite of the slow basal pulse rate at the end of digitalization, the only evidence of intoxication was the presence of ventricular premature beats during rest after exercise. In addition to subjective evidence of increased exercise tolerance, the control of the heart rate response to exertion and the increased vital capacity indicate that the digitalis bodies were beneficial. Fig. 4 indicates that the two preparations are similar. None of the other observations showed any difference in action between the two preparations.

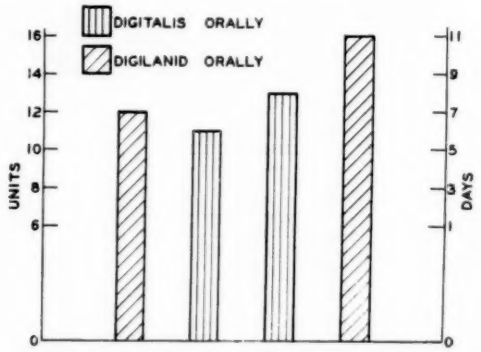

Fig. 3.—Patient A. D. Each bar indicates the digitalizing dose in units of the preparation, and the length of time over which it was administered. The units, method of administration, and criterion of digitalization are described in the text. Four weeks elapsed between the end of each period of digitalization and the beginning of the next.

Additional patients digitalized.—Of the fifty-three remaining patients, twenty-nine were digitalized in the hospital and two in the outpatient department (Table I). These thirty-one were given digilanid to the point of digitalization as ascertained clinically, that is, either by a therapeutic response to the drug, or the induction of toxic symptoms, always either nausea or premature beats. In the group there were six patients with rheumatic heart disease; three with syphilitic heart disease; eleven with hypertensive heart disease, all of whom had some degree of arteriosclerosis; eight with arteriosclerotic heart disease without hypertension; one with thyrotoxic heart disease, perhaps complicated by arteriosclerosis;

one with toxic myocarditis; and one who was found not to have heart disease. Ten had auricular fibrillation. The severity of the heart failure ranged from mild to severe. Only one patient did not have heart failure. Three had angina pectoris. Three were known to have had coronary occlusion. Some were digitalized slowly, and some rapidly. Although direct comparisons were not made in this group, the effect of digilanid seemed indistinguishable from that which would have been expected from the leaf. Eight other patients were given partially digitalizing doses, but the administration was interrupted for various reasons before there was evidence of digitalization. None of these reasons impugned the reliability of digilanid as a digitalis preparation.

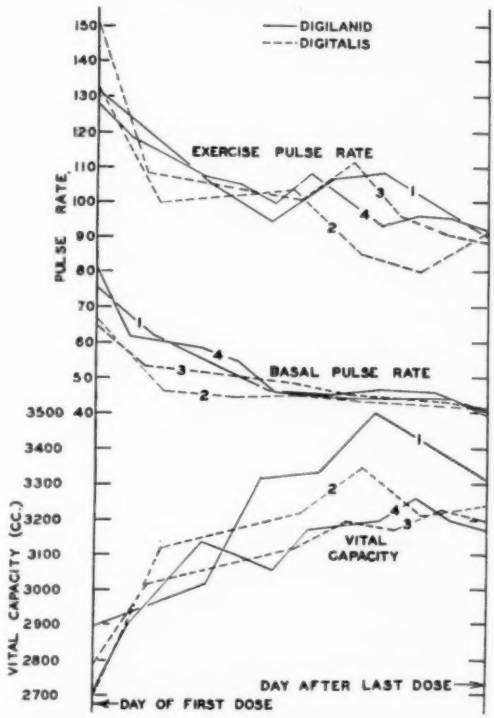

Fig. 4.—Patient A. D. Curves of pulse rate and vital capacity during digitalization with digilanid and digitalis leaf orally. The "exercise pulse rate" was counted for one minute, beginning fifteen seconds after exercise. The time scales of these curves are adjusted in the same way as those of Fig. 2. The numbers on the lines indicate the order of the digitalizations. Lines with the same number correspond.

Maintenance with digilanid.—Twenty-three patients received maintenance doses of digilanid for various periods in the hospital and outpatient department. Ten of these were digitalized with digilanid. The maintenance dose for six of the ten was 1 unit daily; two required 2 units daily, one required 12 units a week, and one required only 3 units a week. The length of observation on the maintenance doses ranged from five weeks to four months; only two of the ten were followed for less than two months.

Thirteen patients were changed from maintenance with the powdered leaf to maintenance with digilanid. The duration of the digitalis administration varied from three weeks to eight years, that of digilanid from three weeks to fourteen months. Ten of the thirteen were observed for more than six months while they were taking digitalis, and for more than three months while taking digilanid, so that significant comparisons of the two drugs could be made. All of the thirteen patients were changed from digitalis to an equal unit dose of digilanid without evidence of any difference in the effect of the two preparations. Three of these patients were of particular interest because untoward symptoms or signs occurred within the range of therapeutic effect. All three had auricular fibrillation. Patient J. A., Unit No. 36600, had an apical rate which was usually above 130 when he was not taking digitalis. There were some ventricular premature contractions whether or not he was taking digitalis. One unit daily reduced the pulse rate to between 100 and 110 per minute. Eight units a week held the rate between 90 and 100 per minute. Nine units a week gave rise to almost complete pulsus bigeminus, with reduced exercise tolerance. Doses were changed and pulse rates counted at intervals of a month. Testing at each of these dosage levels twice with each of the preparations showed no significant difference between them. The optimum dose, so far as comfort was concerned, was 8 units a week of either preparation. In the case of patients A. K., Unit No. 114907, and E. S., Unit No. 115351, 3 units a week were an adequate maintenance dose. Four units a week caused rates between 50 and 60 per minute, and dull, continuous, precordial aching. By repeated trial this phenomenon was found to occur with either preparation in both patients.

Possible discrepancies between the preparations.—Three incidents were observed in which the reactions of individuals to the two preparations were not identical. These were hard to evaluate and will therefore be presented in detail. One concerned H. H., Unit No. 202350, the only patient to receive digilanid who is not included in the above groups. He had hypertension and arteriosclerosis, with cardiac and renal insufficiency. He received powdered digitalis leaf irregularly for six weeks; then, after having had none for seven days, he was given 2 units twice daily for twelve days, from Aug. 30 to Sept. 10, 1938. From Sept. 6 to Sept. 10, he was nauseated immediately after each dose for less than an hour. On the evening of Sept. 10 he was given a placebo of sucrose in a capsule identical with the digitalis capsule, and had no nausea. Two hours later two units of digilanid were given, and it was continued in the same dose as the leaf; the dosage pattern was not interrupted in making the placebo test. The digilanid was continued for four days, without nausea. Unfortunately this could not be repeated, because he died a few hours after the onset of mesenteric thrombosis, Sept. 14. It should be emphasized that this was not the usual nausea of digitalis intoxication, but occurred only within an hour after each dose of the leaf. Patient C. J., Unit No. 176141, had rheumatic heart disease, had had fail-

ure repeatedly, and had taken digitalis over a number of years. When she took digilanid she avoided the very minor abdominal discomfort, with belching, which occurred immediately after taking the powdered leaf. Patient M. P., Unit No. 2129, who had rheumatic heart disease, was changed from a maintenance dose of digitalis leaf to one of digilanid. After a month she insisted on returning to the leaf because digilanid made her left arm stiff. She would not consent to further trial with the drug. She did not remember how long after the change the stiffness appeared.

DISCUSSION

The similarity of digilanid and the powdered leaf which we used, unit for unit, under clinical conditions, is striking. Comparisons of dosage were made on the two patients repeatedly digitalized in the hospital and on the ten patients who were observed for considerable periods on maintenance doses of each preparation. Patient A. H. required a little less, and patient A. D. a little more, digilanid than digitalis leaf, on the average, but the differences were not significant. No difference in dosage requirement was observed in the patients who received a maintenance dose of both drugs. Since the powdered leaf was measured according to the U. S. P. XI unit, which is equal to approximately 1.3 cat units, a difference in dose was expected. It is not possible to say whether this is the result of a difference between the relation of the human therapeutic to the lethal animal dose for the two preparations, such as Bauke[12] observed, or of inaccuracies of "clinical standardization." The same, wide, individual variation in dose that is common with powdered leaf preparations was observed with digilanid. This is well exemplified by the difference in the requirements of patients A. H. and A. D., as indicated in Figs. 1 and 3, and by the doses indicated in Table I.

The effectiveness of the digilanid was the same as that of the powdered leaf throughout the series in so far as comparisons were justifiable; this includes the two patients who were repeatedly digitalized and carefully studied. Although some of the patients were not benefited by full digitalization, this was to have been expected. Patient No. 29 (Table I) was an example of those receiving no benefit. She had hyperthyroidism with heart failure. The basal metabolic rate varied between +48 and +68; she became progressively worse during her seven weeks in the hospital, and died, although continuous effort was made to prepare her for surgical intervention. Death resulted from thyroid crisis. Twelve units of digilanid were given over a period of three days, without any effect on the heart failure, and the drug was stopped because of vomiting. No attempt was made to give it again because it was felt that the reduction of caloric intake incident to the nausea and vomiting more than cancelled any slight benefit that might have accrued from its further use. Such incidents as this do not, of course, indicate that digilanid is inferior, for they are common with other digitalis preparations.

TABLE I

PATIENTS DIGITALIZED ONCE WITH DIGILANID

NO.	AGE AND SEX	ETIOLOGIC DIAGNOSIS	AURICULAR FIBRILLATION	COMPLICATING CONDITIONS	DIGITALIZATION		DIGITALIS WITHIN PRECEDING 3 WK.	IMPROVEMENT IN HEART FAILURE	ROLE OF DIGILANID	REMARKS
					NO. OF 1/3 MG. TABLETS	TIME CONSUMED (DAYS)				
1	36F	Rheumatic	+	----	16	4	0	Good	Definite	Digilanid nausea. Symptoms only on exertion.
2	28F	Rheumatic	+	----	25	13	+	Good	Definite	Auricular fibrillation started during digitalization.
3	45F	Rheumatic	+	----	13	5	+	Good	Definite	
4	40F	Rheumatic	+	----	18	6	0	Good	Definite	
5	53M	Rheumatic	+	----	18	6	0	Good	Definite	Digilanid nausea.
6	30F	Rheumatic	0	----	54	32	0	Fair	Questionable	
7	52M	Syphilitic	0	----	10	2	0	Fair	Questionable	
8	48M	Syphilitic	0	----	18	4	0	Good	Definite	
9	31M	Syphilitic	0	----	161	82	0	Fair	Definite	Symptoms only on exertion. At end of digilanid course he did not have his usual rapid palpitation but complained of slow hard beating.
10	61M	Arteriosclerotic	+	----	44	16	0	Good	Definite	
11	68F	Arteriosclerotic	0	Senile dementia	16	9	+	Good	Definite	
12	54F	Arteriosclerotic	0	Old coronary occlusion	10	6	+	Fair	Definite	Angina in addition to heart failure.
13	63M	Arteriosclerotic	0	Old coronary occlusion	20	5	0	Fair	Definite	
14	73M	Arteriosclerotic	0	Recent coronary occlusion	14	4	0	Good	Definite	Angina in addition to heart failure.
15	65M	Arteriosclerotic	+	Bronchopneumonia Alcoholism	17	4	0	Digilanid given with improvement in heart failure during early days of bronchopneumonia with fatal termination.		

16	63M	Arteriosclerotic	+	----	10	5	?	Good	Definite	
17	65F	Arteriosclerotic	0	Anemia	18	5	0	Good	Questionable	
18	31M	Hypertensive Arteriosclerotic	0	----	42	19	0	Good	Definite	
19	66F	Hypertensive Arteriosclerotic	+	----	17	5	0	Good	Definite	
20	67F	Hypertensive Arteriosclerotic	+	----	30	8	0	Fair	Definite	
21	49F	Hypertensive Arteriosclerotic	0	Beginning uremia	20	5	0	Poor	None	Rate slowed by digilanid.
22	53F	Hypertensive Arteriosclerotic	0	----	16	4	0	Good	Definite	
23	58M	Hypertensive Arteriosclerotic	0	----	24	9	0	Fair	Questionable	Angina in addition to heart failure.
24	71F	Hypertensive Arteriosclerotic	0	----	14	6	+	Good	Definite	Vomiting, probably not due to digilanid.
25	39F	Hypertensive Arteriosclerotic	0	Uremia Anemia	18	5	0	Poor	None	Nausea and vomiting due to uremia or digilanid.
26	50M	Hypertensive Arteriosclerotic	0	Uremia	11	5	+	Poor	None	Rate slowed.
27	48M	Hypertensive Arteriosclerotic	0	Anemia	15	5	0	Fair	Definite	
28	49F	Hypertensive Arteriosclerotic	0	----	84	42	0	Fair	Definite	Symptoms only on exertion.
29	59F	Thyrotoxic	0	Thyrotoxicosis	10	2	0	Poor	None	Vomiting due to digilanid.
30	28F	Toxic	0	Bronchopneumonia	37	15	0	Good	Definite	Heart failure appeared during pneumonia.
31	64M	No cardiac disease	0	Dermatomyositis	24	6[1]	0	Edema not due to heart failure. Digitalized to the point of nausea, as a diagnostic test, before diagnosis was made.		

Symptoms and signs of heart failure were present in these patients with the exceptions noted under remarks. Some were digitalized rapidly and some very slowly as indicated by the "time consumed." Patients 9 and 28 were digitalized in the outpatient department, the others in the hospital. "Improvement in heart failure" refers to the result of total treatment which included other treatment than digitalization. Under the heading "Role of digilanid," "Definite" indicates that there was evidence that digitalization accomplished some improvement in addition to other therapy. "Questionable" indicates that while the patient improved during or after digitalization the influence of digilanid could not be evaluated apart from other treatment.

This study indicates that there is no significant difference between the two preparations tested with respect to the relation of the effective dose to the dose giving rise to symptoms or signs of intoxication. The only apparent differences are noted above. In the two cases in which the leaf produced gastrointestinal symptoms and the digilanid did not, there was probably local irritation without true intoxication. It has been observed repeatedly that various extracts are less likely to cause local irritation than is the whole leaf. The isolated instance in which digilanid caused stiffness of the arm is almost certainly not significant. The two patients who were repeatedly digitalized were carried to the point of minor toxic symptoms each time, and there was no difference between the two preparations with respect to the type or severity of these symptoms. In the three patients who suffered minor toxic symptoms within the range of therapeutic effect and in which comparisons were made, the two preparations acted identically.

SUMMARY AND CONCLUSIONS

A clinical study of digilanid was undertaken because, according to the literature, it possesses advantages over the powdered leaf, in that increased accuracy and uniformity of dosage, gravimetrically determined without biologic standardization, are possible, and that it is highly stable.

Judging from the results of administering the drug to fifty-six patients, including two who were studied under controlled conditions for long periods, it is concluded that digilanid is a potent digitalis preparation, equal in clinical effectiveness to a standard preparation of the powdered leaf.

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BACTERIAL ENDOCARDITIS SUPERIMPOSED ON SYPHILITIC AORTIC VALVULITIS

A Review of the Literature and a Presentation of Five Cases

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INTRODUCTION

SYPHILIS of the aorta and of the aortic valves has been described as a rare predisposing cause of bacterial endocarditis, whereas valvular damage caused by rheumatic fever and congenital abnormalities have been recognized generally as playing a definite role in the formation of vegetations on the endocardium. In reviewing the literature, reports of 1,255 autopsy cases of endocarditis were found; syphilis of the aorta occurred in only 1.3 per cent of these cases (Table I).

Recent experience at the Cincinnati General Hospital has indicated that the coincidence of these two diseases is somewhat more common than has been generally reported. In order to ascertain whether or not this was true, all cases of patients who died between Jan. 1, 1936, and Jan. 1, 1939, in which the diagnosis of bacterial (nonrheumatic) endocarditis was made at autopsy, were reviewed. There were forty-eight cases of acute, and thirty-six cases of subacute, bacterial endocarditis, making a total of eighty-four cases of both types. Among these cases, syphilis of the aorta was found eighteen times. This is an incidence of 21.4 per cent, as compared with that of 1.3 per cent reported in the literature.

REVIEW OF PUBLISHED REPORTS OF BACTERIAL ENDOCARDITIS IN CASES OF SYPHILITIC AORTITIS

In addition to the reported incidence of syphilis in series of cases of bacterial endocarditis (Table I), twenty-seven reports of cases in which

Table I

Incidence of Syphilitic Aortitis in Cases of Bacterial Endocarditis

Horder[1]	1908	2 cases of aortitis among	150 cases of bacterial endocarditis.
Kastner[2]	1918	1 case of aortitis among	16 cases of bacterial endocarditis.
Blumer[3]	1923	0 case of aortitis among	150 cases of subacute bact. endocarditis.
Morrison[4]	1927	3 cases of syph. ht. dis. among	171 cases of bacterial endocarditis.
Thayer[5]	1926	3 cases of aortitis among	198 cases of bacterial endocarditis.
Clawson[6]	1924	0 case of aortitis among	220 cases of bacterial endocarditis.
Smith[7]	1937	3 cases of aortitis among	193 cases of bacterial endocarditis.
Martin[8]	1938	5 cases of aortitis among	157 cases of bacterial endocarditis.
		17 cases	1,255 cases (1.3 per cent)

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there was a combination of syphilitic *aortitis* and bacterial endocarditis were found in the literature. These are listed in Table II.

TABLE II

AUTHORS PUBLISHING CASE REPORTS OF BACTERIAL ENDOCARDITIS IN COMBINATION WITH SYPHILITIC AORTITIS

1918	Kastner[2]
1922	*Briggs[9]
1925	Landau and Held[10]
1927	Cade[11]
1926	Pineles[12]
1927	Gallavardin and Gravier[13]
1928	Steinberg[14]
1928	Sumbral[15] (two cases)
1929	Skursky[16] (two cases)
1931	Lemann[17]
1931	Schnabel and Leivy[18]
1932	*Craven[19]
1934	Brahic, Recordier, and Sarradon[20]
1934	Francois and Jouve[21]
1935	*Raybaud and Jouve[22]
1935	Areta[23]
1937	*Smith[7] (three cases)
1937	*McMillan and Wilbur[24]
1938	*Martin and Adams[8] (five cases)

*Judging from the descriptions given, these reports included cases of syphilitic aortic *valvulitis*, as well as syphilitic *aortitis*, with superimposed bacterial endocarditis. They are summarized in Tables III and IV.

In order to state that there is any causal relationship between syphilis and bacterial endocarditis, it was felt that, first, syphilitic aortic valvular disease must be demonstrated, and, second, that the vegetations must involve this valve. Certainly, it is difficult to understand how syphilitic disease of the first part of the aorta could predispose to the formation of vegetations on the aortic valve when this valve, both grossly and microscopically, is not affected by the syphilitic process. Furthermore, since rheumatic scarring of the aortic, and particularly of the mitral, valve is such a common precursor of bacterial endocarditis, it was felt that, no matter how extensive the syphilitic process might be, if any of the stigmata of rheumatic heart disease were present, the predisposing cause of the endocarditis was more likely rheumatic than syphilitic.

Of the twenty-seven case reports included in Table II, only six contained satisfactory gross and microscopic descriptions supporting the diagnosis of syphilitic aortic valvulitis. These are summarized in Tables III and IV. In some there was a definite statement that the aortic valves showed no evidence of syphilis; in others, thickening of the mitral valve which suggested rheumatic valvular damage was described.

Unfortunately, in the cases reported by Kastner, Landau and Held, Skursky, Schnabel and Leivy, Areta, Sumbral, and Lemann there was no accurate description of the aortic valves, and, although valvulitis may very well have been present, these cases could not be included in

this study. In the reports by Pineles and by Steinberg, and in that of Smith's first case, there were definite statements that the aortic valves were normal. In the cases of Brahic, Recordier, and Sarradon, and Francois and Jouve there was gross evidence of pre-existing disease of the mitral valve. Smith, in describing his third case, reports that it was impossible to say whether the predisposing cause of the endocarditis was rheumatic heart disease or syphilis, since both were present. From the microscopic descriptions in the case reported by Cade, it was impossible to rule out rheumatic endocarditis. In the case of Gallavardin and Gravier there were vegetations on a foldlike structure in the aorta a short distance above the aortic valves. It has not been included in the summary because the aortic valve itself was free of vegetations.

Recently, Martin and Adams[8] reported 157 cases of vegetative endocarditis in a series of 17,000 autopsies, but in only five of these was there syphilis of the aorta or of the aortic valve. In one of the five cases there was also rheumatic heart disease, and in two others the syphilitic and bacterial lesions were located in the aorta and not on the aortic valve. In a fourth case the presence of massive, fibrinous pericarditis and the lack of microscopic sections made the etiology of the aortic valve lesion uncertain. Therefore, only one of the five cases of Martin and Adams is included in the clinical and pathologic summaries in Tables III and IV.

CRITERIA FOR THE DIAGNOSIS OF SYPHILITIC AORTITIS AND SYPHILITIC VALVULITIS IN CASES OF BACTERIAL ENDOCARDITIS

Certain pathologic criteria were established for the selection of cases from the autopsy material at the Cincinnati General Hospital. The criteria for a diagnosis of *syphilitic aortitis* were as follows:

(1) Periarteritis of the vasa vasorum in the adventitia, with lymphocytes and plasmatocytes as the predominating infiltrating cells.

(2) Some extension of this process to the media.

There was usually some endothelial proliferation in the intima of the vasa vasorum. The process in the media always presented some destruction of elastic tissue, either by necrosis with abundant inflammatory reaction, or, in the later stages, by vascularized scar tissue with less active inflammation.

The criteria for *syphilitic aortic valvulitis* were:

(1) Periarteritis, and other changes as above described, in the base of the valve and in the adjacent sinus of Valsalva.

(2) If no valvular arterioles were included in the sections available, then, in addition to the syphilitic aortitis in the sinus of Valsalva, there must have been either vascularized scar tissue with lymphocytic infiltration in the base of the valve, or extensive scarring of the valve, producing the typical gross picture of rolling of the free edges of the valve cusps, with retraction downward from the coronary orifices.

TABLE III

CLINICAL SUMMARY OF CASES OF SYPHILITIC AORTIC VALVULITIS AND BACTERIAL ENDOCARDITIS

CASES FROM THE LITERATURE	AGE, SEX, AND RACE	SYPHILITIC HISTORY	RHEUMATIC HISTORY	HISTORY OF HEART DISEASE	DURATION OF FEVER	SEROLOGIC REACTION	BLOOD PRESS.	DESCRIPTION OF HEART	BLOOD CULTURE
Briggs 1922	35, male, white	Chancre 20 years before death, no secondaries, treatment with salvarsan and mercury salicylate 4 years before death.	None	A to-and-fro murmur described 4 years before death, angina 3 years before.	5 months	Wass. +++	120/40	Enlarged to the left, a to-and-fro murmur over the base, a loud systolic, and a soft diastolic murmur over the apex.	ante mort: nonhemolytic streptococcus post mort: none recorded
Craven 1932	23, male, colored	Chancre 4 years before death followed by a generalized rash. Six injections of arsphenamine before rash and six after.	Frequent sore throats but no joint symptoms	Dyspnea 4 months before death. Diagnosis of syphilitic aortitis made at this time.	Not known but less than 4 months.	Wass. +++	190/50	Apex impulse 14 cm. from the midsternal line, a systolic murmur all over the precordium, a loud diastolic murmur over base.	ante mort: none recorded post mort: *Streptococcus viridans*
Raybaud 1935	50, male	Chancre 30 years before death, followed by several years of "specific treatment."	Fleeting joint pains with onset of fever, no previous history.	3 years before death a to-and-fro murmur was described.	6 months	Wass. neg.		A systolic murmur all over the precordium, and a loud diastolic murmur over the base.	ante mort: nonhemolytic nonpigment forming streptococcus post mort: none recorded
Smith 1937	63, male, white	None	None	None	Over 13 days	Kahn +++	118/55	Heart not enlarged, a harsh systolic murmur heard all over the precordium, no diastolic murmurs heard.	ante mort: *staph. albus* post mort: *Staph. albus*

McMillan 1937	47, male, white	Chancre 30 years before death, 6 injections of arsphenamine 16 years before death.	None	Precordial pain for 5 years before death, later dyspnea edema and congestive failure.	Not known	Kahn +++	170/70	Heart greatly enlarged, a loud systolic and a loud diastolic murmur heard all over the precordium.	ante mort: none recorded post mort: *Staph. aureus*
Martin 1938	51, male, white	Chancre 46 years before death, no treatment.	None	Dyspnea 2 years before death	2 days	Wass. +++ Kahn +++	175/34	Heart enlarged to left and downward. Diastolic murmur over the mitral area, a to-and-fro murmur over the base.	ante mort: none recorded post mort: *Streptococcus viridans* from tissue culture.
CASES FROM CINCINNATI GENERAL HOSP.									
Case 1 (55923)	36, male, colored	No primary or secondary, but 2 years before death had "bad blood." 2 injections of neoarsphenamine.	Joint pains 24 yrs. before death, never very severe.	Dyspnea one year before death.	5 weeks	Kahn +++	130/70	Enlarged, a systolic murmur over the apex and a diastolic murmur over the base.	ante mort: *Streptococcus viridans* post mort: none taken
Case 2 (62584)	33, female, colored	Chancre 11 years before death. 1 year of treatment.	Rheumatism of both knees 27 years before death.	Angina and dyspnea 1 year before death, diagnosis of syphilitic aortitis made at this time.	7 weeks	Kahn neg. Wass. neg.	120/40	Enlarged, a diastolic thrill felt all over the precordium, a systolic and diastolic murmur heard all over the precordium.	ante mort: 4 cultures were negative post mort: none taken

TABLE III—CONT'D

CASES FROM THE LITERATURE	AGE, SEX, AND RACE	SYPHILITIC HISTORY	RHEUMATIC HISTORY	HISTORY OF HEART DISEASE	DURATION OF FEVER	SEROLOGIC REACTION	BLOOD PRESS.	DESCRIPTION OF HEART	BLOOD CULTURE
Case 3 (71684)	53, female, colored	Several miscarriages, otherwise negative.	None	None	11 weeks	Kahn +++	140/0	To-and-fro murmur all over the precordium.	ante mort: *Streptococcus viridans* post mort: none taken
Case 4 (88858)	41, female, colored	No history of primary or secondary. Strongly positive Kahn 2 years before death.	None	Dyspnea and orthopnea 6 weeks before death, followed by anginal pain.	Not known	Kahn +++	130/30	Enlarged, a systolic murmur and a soft diastolic murmur over the aortic area, no murmurs over the apex.	ante mort: *Bacillus bronchisepticus* post mort: *Bacillus bronchisepticus*
Case 5 (103566)	29, male, white	Chancre 9 years before death, followed immediately by 5 injections of neoarsphenamine. 6 more injections 1 year before death.	None	Dyspnea 8 months before death. Was diagnosed as aortic regurgitation.	4 months	Kahn +++	92/42	Enlarged, a to-and-fro murmur over the aortic area.	ante mort: 4 neg. cultures post mort: (contaminated) *Strep. viridans, Staph. aureus,* and *B. coli.*

TABLE IV

PATHOLOGIC SUMMARY OF CASES OF SYPHILITIC AORTIC VALVULITIS AND BACTERIAL ENDOCARDITIS

CASES FROM THE LITERATURE	WEIGHT OF HEART	DESCRIPTION OF AORTA	DESCRIPTION OF AORTIC VALVE		DESCRIPTION OF MITRAL VALVE	OTHER VALVES	RHEUMATIC STIGMATA
			SYPHILITIC LESION	BACTERIAL LESION			
Briggs 1922	550 Gm.	Striations of the intima within the first 4 cm. of the aorta, thickness greater than normal. Also atheromatous plaques.	Separation of the aortic cusps, but no other thickening or deformity.	Large yellow brown verrucose masses of soft friable material.	Vegetations of the anterior leaflet by direct extension from the aortic valve.	Normal measurements but not otherwise described.	None mentioned.
Craven 1932	630 Gm.	A wrinkled patch 1 cm. above the posterior cusp, deep scars in the media and thickening of the intima. Micro: fibrous tissue in the adventitia and perivascular infiltration with lymphocytes.	Valves retracted and shortened with a thickened irregular edge. Micro: scarring, vascularization and lymphocytic infiltration.	On the posterior cusp soft friable pinkish-grey vegetations with a perforation of one cusp.	A few small protuberances juxtaposed to the aortic valve, otherwise completely negative.	Pulmonary and tricuspid show no abnormalities.	No scars or leucocytic infiltrate in the myocardium.
Raybaud 1935		Endarteritic plaques in aortic wall, Micro: perivascular infiltration of the wall of the aorta.	No gross description of the valve was given, but there was lymphocytic infiltration of the aortic ring and the base of the aortic valve.	Vegetations on the aortic valve.	A few small vegetations, otherwise completely negative.	Not mentioned.	None mentioned.
Smith 1937		Puckering and linear striations of the base of the aorta. Micro: scars with infiltration with round and plasma cells.	Separation of the commissures. Micro: round and wandering cells in the media.	Ulcerative endocarditis on the posterior and right cusps with friable vegetations. Micro: fibrous deposits without much vascularization.	Grossly normal, no microscopic description given.	Normal measurements, no other description.	None mentioned.

TABLE IV—CONT'D

CASES FROM THE LITERATURE	WEIGHT OF HEART	DESCRIPTION OF AORTA	DESCRIPTION OF AORTIC VALVE		DESCRIPTION OF MITRAL VALVE	OTHER VALVES	RHEUMATIC STIGMATA
			SYPHILITIC LESION	BACTERIAL LESION			
McMillan 1937	750 Gm.	An aneurysm 8 cm. in diameter in the first part of the aorta. Micro: scars and infiltration with round cells in the adventitia.	Separation of the cusps. Micro: much fibrous thickening.	Wartlike vegetations near the free edge of the cusp, granulation tissue and debris seen microscopically.	Vegetations opposite the aortic valve, otherwise negative.	Not described.	None mentioned.
Martin 1938	750 Gm.	Moderately dilated, numerous small atheromatous areas and plaques with longitudinal wrinkling. Micro: fibrous thickening of the intima, round-cell infiltration of the media, perivascular infiltration of vasa vasorum.	Incompetent by water test, slight thickening and rolling of edges of all cusps, retraction downward and spreading of the cusps. Micro: no report.	Perforations in the right and posterior cusp, surrounded by small friable vegetations. Mycotic aneurysm of pars membranacea. Micro: no report.	Ring moderately dilated, leaflets slightly thickened, perforation of the posterior leaflet.	Tricuspid dilated.	None mentioned, no microscopic findings given.
CASES FROM CINCINNATI GENERAL HOSPITAL							
Case 1 N-36-336	475 Gm.	Numerous syphilitic plaques, with narrowing of the right coronary orifice. Micro: typical syphilitic lesion with scars.	Slightly rolled edges with double insertions. Micro: vascularized scar tissue with lymphocytes at the base and proximal portion.	Large shaggy vegetations. Micro: *Strep. viridans* subacute inflammation.	Some atherosclerosis, and some vegetations with extensive inflammation.	Not remarkable.	Absent.

Case 2 N-36-682	440 Gm.	Typical plaques with narrowing of the right coronary orifice. Micro: moderate lesions in the adventitia with slight scarring in the media.	Retracted cusps with rolled edges, low insertions. Micro: active lesions with moderate scarring.	Subacute vegetations on one cusp and on the mural endocardium. Micro: subacute inflammation.	Base only involved by direct extension, no scarring.	Not remarkable.	Absent.
Case 3 N-37-246	430 Gm.	Typical syphilitic plaques, also arteriosclerosis with calcification and ulceration. Micro: typical lesions of syphilis and arteriosclerosis.	Firm distorted cusps with double insertions. Micro: typical lesions at the base of the valve, also subacute inflammation, scarring and atherosclerosis.	Cusps extensively ulcerated and covered with large vegetations, one cusp perforated. Micro: subacute inflammation.	Extensive subacute inflammation by direct extension. No scarring.	Not remarkable.	Absent.
Case 4 N-38-128	360 Gm.	Typical plaques of sypilis, also some arteriosclerosis. Micro: typical lesions of spyhilis.	Firm distorted cusps with double insertions. Micro: active lesions of one cusp and scarring of another.	One medium sized vegetation, other smaller ones Micro: acute ulcerative endocarditis (*Bacillus bronchosepticus.*)	Not remarkable	Not remarkable.	Absent.
Case 5 N-38-503	515 Gm.	Small plaques and beginning aneurysm in the sinus of Valsalva. Micro: very active syphilitic lesions with little scarring. Miliary gumma.	Cusps eroded, scarring not recognized. Micro: scarring at the base of the valve and in the proximal portion, very active lesions at the base and in pars membranacea.	Small vegetations becoming confluent; ulceration and organization. Micro: subacute bacterial inflammation with miliary abscesses, numerous gram negative unidentified organisms.	Subacute bacterial inflammation by direct extension also miliary abscesses, no scarring.	Not remarkable.	Absent.

The stigmata of rheumatic heart disease which were looked for were:

(1) Aschoff bodies in any stage of development or evolution, including the late scar stage, i.e., nodules or rings of fibrous tissue in the adventitia of small coronary arteries.

(2) Scarring of the mitral valve predominantly along the line of closure, or producing any degree of stenosis.

(3) Thickening of the endocardium of the left atrium in the manner so often seen in chronic rheumatic heart disease.

(4) Adhesive pericarditis.

CASE REPORTS

Of our eighteen cases of syphilitic aortitis and bacterial endocarditis, seven were excluded because of the presence of aortitis alone, without syphilitic aortic valvulitis, or because the ulceration of the valve was so extensive that, although syphilis of the valve was suspected, it could not be definitely diagnosed. In five of the cases rheumatic stigmata, as well as syphilitic disease of the aortic valve, were found. In one case of typical syphilitic valvulitis, with a gumma involving the left ventricular wall, the bacterial lesions were caused by *Salmonella suipestifer*. They were superimposed upon the gumma and did not involve the aortic valve. This case has been reported by Forster. The remaining five cases are considered to be examples of bacterial endocarditis superimposed on syphilitic aortic valvulitis, with no evidence of congenital or rheumatic heart disease. These are described in detail, and summaries can be found in Tables III and IV.

CASE 1.—C. O., a 36-year-old colored laborer, was admitted to the medical service for the first time on May 7, 1936, with the chief complaint of "pains in the joints." In March, 1936, his illness began with cough and fever which persisted for one month. He was then forced to stop work because of pains in his knees and ankles, and slight dyspnea on exertion. During the following month he experienced night sweats, headaches, and felt feverish. The past history revealed that at the age of 17 (19 years before admission) he had had a similar attack of joint pains that were never severe enough to confine him to bed. There was no history of chancre or secondary eruption, but several years before admission he was told that he had "bad blood"; he received two intravenous injections, after which treatment was discontinued.

On admission the temperature was 100.5° F., the pulse rate 120, and the respiratory rate 24. He was a well-developed and well-nourished middle-aged colored man, lying flat in bed. No petechiae were noted. The lungs were normal. The heart was slightly enlarged. At the apex there was a loud, blowing, systolic murmur which was transmitted into the axilla; over the base this same systolic murmur was heard, and there was also a soft, diastolic murmur which was transmitted down the sternum. The blood pressure was 130/70. The abdomen was soft, and none of the solid organs could be felt. Both knees and ankles were painful, hot, and swollen, which symptoms were suggestive, but not diagnostic, of rheumatic fever. The pulses were everywhere normal.

Laboratory Examination.—The erythrocyte count was 3,750,000; the hemoglobin was 11 Gm. The leucocyte count ranged between 10,000 and 17,000, and there

was a predominance of polymorphonuclears. One urine specimen was essentially normal; it contained no erythrocytes. The blood Kahn reaction was positive (+++). A teleoroentgenogram showed that the retrosternal width at the second interspace was 6.5 cm., the greatest cardiac width, 16.5 cm., and that the width of the chest was 30 cm. The electrocardiogram showed low voltage T waves in all leads, and a prominent Q_3. Three blood cultures were taken; one was negative, and two were positive for *Streptococcus viridans*.

A diagnosis of rheumatic heart disease, mitral and aortic insufficiency, and subacute bacterial endocarditis was made. On the twenty-first day the patient left the hospital against the advice of his physician. One month later he returned in a very critical condition, and died within a few hours after admission.

The autopsy was performed twenty-two hours post mortem. The final gross and microscopic diagnoses were as follows: subacute *Streptococcus viridans* endocarditis of the mitral and aortic valves, with miliary abscesses in the myocardium; marked syphilitic aortitis, with extension into the sinuses of Valsalva, partially occluding the right coronary orifice, and into the base of the aortic valve; extensive myocardial fibrosis; myocardial hypertrophy and dilatation; chronic passive congestion of the lungs and the abdominal viscera; central necrosis of the liver; early, generalized, vascular sclerosis, with beginning arteriolonephrosclerosis; acute purulent meningitis; and acute splenitis.

The heart weighed 475 grams. All chambers were dilated. The epicardium and the tricuspid and pulmonary valves were not remarkable. There were small patches of atheroma on the leaflets and chordae tendineae of the mitral valve; this valve measured 120 mm. in circumference. The leaflets presented many friable, yellowish-pink, adherent masses of vegetations.

The cusps of the aortic valve had thickened, slightly rolled margins, and double insertions. Two of the cusps were greatly distorted and covered by large, shaggy, soft masses of vegetations. There were numerous pearly-white plaques, with longitudinal wrinkling, in the aorta, especially in the thoracic portion. Typical atherosclerotic plaques were present also. The white plaques extended into two of the sinuses of Valsalva and had produced a smooth, white thickening around the orifice of the right coronary artery.

Microscopically, there were typical syphilitic lesions in the thoracic aorta, in the sinuses of Valsalva, and at the bases of two of the aortic cusps. The distal portions of these cusps were extensively ulcerated, infiltrated with inflammatory cells, and covered by bacterial vegetations, so that, if there was a syphilitic process beyond the base and proximal portions of the cusps, its presence could not be detected. The third cusp showed no evidence, microscopically, of either active syphilitic inflammation or subacute bacterial endocarditis.

Although the syphilitic lesions in this case contained some areas of marked, active inflammation, the predominating process was one of scar formation. There was extensive scarring of the adventitia of the aorta and of the vasa vasorum. A plaque of scar tissue partially occluded the right coronary orifice. A few nests of lymphocytes were still present in this plaque. The myocardial fibrosis was probably caused by this narrowing of the right coronary orifice.

The bacterial involvement of the mitral valve possibly occurred by extension through the heart wall from the aortic valve (since myocarditis and miliary abscesses were present in the myocardium adjacent to both valves), but there were not enough sections to settle this question.

CASE 2.—M. R., a 33-year-old colored housemaid, was admitted to the neurologic service on Oct. 3, 1936, because of a left-sided hemiplegia. She had been healthy until one year prior to entry, when she complained of pains over her heart and dyspnea on exertion. The diagnosis of syphilitic aortic regurgitation was made at that time. Two months before admission she suddenly collapsed, and since then

had complained of severe precordial pain, dyspnea, and nervousness. Hemiplegia appeared on the morning of admission. She reported that at the age of 22 she noticed a sore on her vulva and several years later was told that she had "four-plus blood." Intravenous and intramuscular injections were given during the ensuing year, at the end of which time she was discharged as cured. At the age of 6 she had had an attack of rheumatism in both knees which confined her to bed for two weeks.

On admission, the temperature was 102°, the pulse rate, 95, and the respiratory rate, 30. She was a middle-aged colored woman, lying in bed in a semicomatose condition, unable to speak coherently or to use her left arm or leg. No petechiae were seen. The heart was enlarged; the apex impulse was visible and palpable in the anterior axillary line. A diastolic thrill could be felt over the entire precordium. A systolic and a diastolic murmur were heard over the entire precordium and in the neck. The blood pressure was 120/40. No abdominal masses could be felt on admission, but during the third week the spleen became palpable. Motor and reflex changes in the face and extremities were indicative of a cerebral lesion in the right parietal region. The joints were normal.

Laboratory Examination.—The erythrocyte count was 3,500,000; the hemoglobin, 10.5 grams. The leucocyte count ranged between 11,000 and 17,000. No erythrocytes were seen in any of the urine specimens. The blood Kahn and Wassermann reactions were negative on two occasions. A teleoroentgenogram showed a slight increase in the size of the heart, without mitral deformity. The electrocardiogram was essentially normal. Four blood cultures were negative.

During the seven weeks of hospitalization, the temperature ranged between normal and 102° F., usually with an afternoon rise. The anemia and weakness progressed, and she died forty-eight days after admission. The final diagnoses were: syphilitic heart disease with syphilitic aortitis, and subacute bacterial endocarditis with embolism of the right, middle, meningeal artery.

The autopsy was performed twenty-one hours post mortem. The final gross and microscopic diagnoses were as follows: cerebral infarction; subacute bacterial endocarditis of the aortic valve, extending through the heart wall to the base of the mitral valve; syphilitic aortitis and aortic valvulitis, with narrowing of the right coronary orifice; marked myocardial fibrosis; myocardial hypertrophy and dilatation; marked pulmonary edema; chronic passive congestion of the viscera; focal embolic glomerulonephritis, with organizing and recent renal infarcts; subacute splenitis; chronic, active, intrahepatic cholangitis.

The heart weighed 440 grams. The epicardium and the mitral, tricuspid, and pulmonic valves presented no gross lesions. The cusps of the aortic valve were retracted and rolled along the free edges, with obliteration of the corpora arantii. The cusps were inserted below the level of the coronary orifices, although the insertions were not double. At the point of insertion of the right and posterior cusps there was a small, friable, pink mass, about one cm. in diameter, which was firmly attached. Small vegetations were also found on one of the aortic valve cusps, whence they extended down over the left ventricular endocardium. The process extended into the heart wall in this area. A microscopic section showed that the inflammatory process had extended to the base of the mitral valve, but did not involve the leaflets. Microscopically, the bacterial lesions showed beginning organization, although the more superficial portions of the lesions were acute. There were typical syphilitic lesions of the aortic valve cusps, with considerable vascularized scarring. The aorta, grossly, presented pearly-gray plaques, with longitudinal wrinkling extending into the sinuses of Valsalva and causing narrowing of the right coronary orifice. Microscopically, the aortic lesions presented the appearance of periarteritis of the vasa vasorum, with beginning involvement of the media. Very little scarring of the media was seen in the available sections.

CASE 3.—F. T., a 53-year-old colored laundress, was admitted to the medical service on March 11, 1937, with the chief complaint of "chills and fever." The present illness started five weeks before admission with generalized malaise, chilly sensations, and fever. On one occasion she was told that her temperature was 104° F. There was no history of anginal pain, dyspnea, orthopnea, or edema, and she had never had joint symptoms. There was no history of a chancre or secondary rash. She had, however, had several miscarriages at about four or five months.

On admission the temperature was 101° F., the pulse rate, 100, and the respiratory rate, 25. She was a thin, middle-aged, colored woman who appeared anemic and chronically ill. No petechiae were seen in the skin, conjunctivae, or mucous membranes. Percussion of the heart showed that the area of retrosternal dullness was 5.5 cm. wide; the apex impulse was forceful, and the left border of dullness extended 8 cm. from the midsternal line. There was a loud to-and-fro murmur which was heard over the base of the heart and down the left border of the sternum. The abdomen was soft, and no solid viscera were palpated. The blood pressure was 140/0.

On admission the erythrocyte count was 2,400,000, and the hemoglobin was 8.0 grams. The leucocyte count never went above 8,000. A few leucocytes were present in all of the urine specimens, and on several occasions erythrocytes were also seen. The blood Kahn reaction was positive (+++). A teleoroentgenogram showed that the greatest cardiac diameter was 14 cm., and the greatest diameter of the chest, 25 cm. The configuration of the heart was not remarkable. The electrocardiogram was essentially normal. Four blood cultures were taken, and all were positive for *Streptococcus viridans*.

During her four weeks' stay on the ward her temperature ranged between normal and 102° F. The erythrocyte count fell in spite of transfusions, and she died of her infection approximately two months after its inception.

The final diagnoses were syphilitic heart disease with aortic regurgitation, and superimposed streptococcus endocarditis.

The autopsy was performed three hours after death. The final gross and microscopic diagnoses were as follows: extensive, subacute *Streptococcus viridans* endocarditis of the aortic and mitral valves, with abscess in the heart wall; miliary abscesses in the myocardium and epicardium; atrial mural thrombosis; extensive syphilis and atherosclerosis, with ulceration and calcification, in the aorta and aortic valve; early miliary abscesses in the brain, lungs, and suprarenal glands; focal, embolic glomerulonephritis; acute splenitis; slight, acute, passive congestion of the abdominal viscera; chronic, hypertrophic, cystic endometritis.

The heart weighed 430 grams. The epicardium and the pulmonary and tricuspid valves were not remarkable. On the aortic valve there were numerous cauliflower-like vegetations which were extending down over the ventricular endocardium. One of the valve cusps had ulcerated through into the sinus of Valsalva. The valvular insertions were double. The cusps felt firm. The aorta near its base was mottled with gray and yellow plaques, some showing longitudinal wrinkling, and others, calcification. The coronary orifices were narrowed by plaques. The bacterial lesion on the aortic valve was traced through the heart wall to the mitral valve, which showed beginning ulceration, but no scarring.

Microscopically, there were typical syphilitic lesions in the aorta, in some places quite active, in other areas scarred. One cusp of the aortic valve was markedly scarred, and in a few areas near the base there was beginning calcification. Sections from the other two cusps showed extensive subacute bacterial valvulitis, with distortion and destruction of valve substance. Near the base of one of these two cusps there was an abscess capped by a large thrombus. At the base of the other cusp there was vascularized scar tissue, including, in some areas, marked scarring of arterioles and typical perivascular lymphocytic collars. Typical syphilitic lesions

also extended backward in the aorta through the sinuses to the bases of the aortic cusps.

The mitral valve, microscopically, presented only one pathologic process, namely, subacute bacterial inflammation.

CASE 4.—E. B. was a 41-year-old colored housewife who, six weeks before admission, developed a sharp, knifelike pain in the left hypochondrium which lasted about ten minutes. Several days later she developed dyspnea, orthopnea, and attacks of pain in the epigastrium and precordium. She later came to the hospital because of severe attacks of paroxysmal, nocturnal dyspnea. There was no history of chancre or secondary rash. Two years before admission, however, she had been treated in the clinic for chronic salpingitis, and was found to have a positive (+++) blood Kahn reaction. The blood pressure was not taken on this visit, nor were the heart findings described. There was no history of rheumatic fever, joint pains, or scarlet fever.

The temperature on admission was 101° F., the pulse rate, 112, and the respiratory rate, 30. The patient was a fairly well-developed, middle-aged colored woman who was obviously quite ill. Orthopnea, dyspnea, and cyanosis were marked. Neither of the pupils reacted to light, but both reacted during accommodation. Ophthalmoscopic examination disclosed early optic atrophy. Dullness, shading off to flatness, was found on percussion of the bases of both lungs; over the area of dullness, coarse, moist râles were heard bilaterally. The apex impulse of the heart was quite diffuse, and the left border of dullness extended 11 cm. from the midsternal line in the sixth intercostal space. Over the aortic area there were a loud systolic murmur and a softer diastolic murmur. No murmurs were heard over the apex. The blood pressure was 130/(?)30. The liver was found to extend three finger-breadths below the right costal margin; no other masses were felt in the abdomen. Very slight edema of the ankles was found.

The erythrocyte count was 4,750,000, and the hemoglobin, 11.2 Gm. Two leucocyte counts were 4,900 and 6,900 respectively; the differential count was normal. The urine was essentially normal. The blood Kahn reaction was positive (+++). The urea nitrogen content of the blood was 34 mg. per cent. A teleoroentgenogram showed that the heart was enlarged in all directions without any characteristic deformity. There was a heavy shadow over the lower half of both lung fields. The aorta was not remarkable. The electrocardiogram showed a P-R interval of .18, an inverted T_1, an isoelectric T_2, and an upright T_3. A blood culture revealed the presence of *Bacillus bronchisepticus*.

The temperature ranged between 100.5 and 101.5° F.; the pulse and respiratory rates gradually rose. The patient failed rapidly, and died on the third hospital day. The final diagnoses were syphilitic aortitis, syphilitic aortic regurgitation, congestive heart failure, and central nervous system syphilis with early optic atrophy.

The autopsy was performed six hours post mortem. The final gross and microscopic diagnoses were as follows: acute, ulcerative, *Bacillus bronchisepticus* endocarditis of the aortic valve; focal necrosis of the myocardium; syphilitic aortitis and aortic valvulitis; slight perivascular fibrosis of the myocardium; myocardial hypertrophy and dilatation; chronic passive congestion of the viscera; bilateral hydrothorax; chronic, active salpingitis and cervicitis; lobular pneumonia.

The heart weighed 360 grams. There was moderate dilatation of the left ventricle. The epicardium and the mitral, tricuspid, and pulmonic valves were not remarkable. A dark-red vegetation, one centimeter in diameter, was found on the ventricular surface of the right anterior cusp of the aortic valve. It had ulcerated entirely through the cusp. The other cusps were thickened, retracted from the coronary orifices, and presented double insertions and minute superficial vegetations.

Both yellow and white plaques were numerous in the aorta. The former contained some calcium, and the latter showed longitudinal wrinkling. The plaques

extended into the sinuses of Valsalva and surrounded the coronary orifices, which, however, were not appreciably narrowed.

Microscopically, the aorta contained typical syphilitic lesions, with perivascular lymphocytic infiltration, vascularized medial scarring, and linear streaks of scar tissue in the adventitia. Similar lesions were found in one of the sinuses of Valsalva. One cusp of the valve was markedly scarred and distorted, with only a small area of fresh, ulcerative endocarditis. Another cusp contained extensive lymphocytic infiltration of vascularized, newly forming scar tissue, and showed acute ulceration of the surfaces, on which there were colonies of Gram-negative bacilli, shown by culture to be *Bacillus bronchisepticus*.

CASE 5.—H. W., a 29-year-old, white, taxicab driver, was admitted to the medical service for the first time on Jan. 8, 1938. He stated that several weeks before admission he had had coryza and a mild cough. Three days later he was seized with pain in his left shoulder, flank, and epigastrium, which was worse on deep inspiration. On admission the temperature was 101.2° F., the pulse rate, 92, and the respiratory rate, 32. Movement of the left side of the chest and diaphragm was limited, but no friction rub and no underlying lung disease could be demonstrated. The heart was enlarged, with the left border of dullness 11.5 cm. from the midsternal line in the sixth intercostal space. There was a to-and-fro murmur at the base which was transmitted down the sternum to the apex. The blood pressure was 144/38. The abdomen was normal, and no petechiae were noted. The leucocyte count was 5,500, and the urine contained a little albumin (1 plus). The blood Kahn reaction positive (+++); the rest of the laboratory findings were negative. No blood culture was taken. A teleoroentgenogram showed nothing except enlargement of the left ventricle. During the first week on the ward, the temperature ranged between 101 and 102° F., and then fell to normal. He was discharged, against the advice of the staff physicians, with the final diagnosis of syphilitic aortic regurgitation. The fever was never adequately explained.

He remained at home in bed for two weeks and then returned to work. From then until his final admission on Aug. 15, 1938, he frequently had to stop work because of feverish spells, weakness, and chills. Dyspnea on exertion became apparent and grew worse as time went on. Shortly before his final admission he developed a cough productive of clear, mucoid material, and edema of the ankles, palpitation, and paroxysmal nocturnal dyspnea appeared.

The past history revealed that nine years before his death he had had a chancre, for which he took local treatment and five intravenous injections. Between the two admissions he received three 0.6 Gm. injections of neoarsphenamine, and eight intramuscular injections of bismuth. Two years before his death he had tularemia, with a lesion on the finger and enlargement of the axillary lymph nodes, but was not sufficiently ill to require hospital care.

Physical examination on the second admission showed that the temperature was 100° F., the pulse rate, 110, and the respiratory rate, 28. He was dyspneic and showed evidences of recent weight loss. The skin was pale and no petechiae were seen, but there was one red, punctate area in the lower portion of the left conjunctiva. The chest was normal except for moist râles at the bases of both lungs. The heart was larger than it had been seven months previously; the left border of dullness extended to the anterior axillary line. The to-and-fro murmur was still present; the aortic second sound was absent. The blood pressure was 92/42. The liver extended 3 cm. below the costal margin; the spleen could not be felt. The erythrocyte count had fallen to 3,130,000; the leucocyte count was 7,800. The blood Kahn reaction was again positive (+++). A teleoroentgenogram showed tremendous enlargement of the heart without any particular type of configuration; the electrocardiogram showed left axis deviation, a P-R interval of .24, and low voltage T waves in all leads.

During his stay in the hospital, the temperature fluctuated between 98° and 102° F., and the urine contained microscopic quantities of erythrocytes on three occasions. The leucocyte count never went above 9,000; the erythrocyte count fell to 2,800,000 in spite of transfusions. Four blood cultures were negative. The spleen became palpable, and, on the sixteenth hospital day, he became extremely dyspneic and died shortly afterward. The final diagnoses were syphilitic heart disease with aortic regurgitation, and probably subacute bacterial endocarditis.

The autopsy was performed nine hours after death. The final gross and microscopic diagnoses were as follows: subacute bacterial endocarditis of the mitral and aortic valves (Gram-negative organism not yet identified); miliary abscesses of the valves and myocardium, with acute interstitial myocarditis; active syphilitic aortitis and aortic valvulitis, with extension to the pars membranacea; myocardial hypertrophy and dilatation; chronic passive congestion of the lungs, spleen, kidneys, and liver; peripheral edema; right-sided hydrothorax; acute and subacute embolic glomerulonephritis; acute splenitis; central zonal hepatitis; early lobular pneumonia; acute hilar lymphadenitis.

The heart weighed 515 grams. The epicardium and the tricuspid and pulmonic valves were not remarkable. There was marked flattening of all of the columnae carneae, with dilatation of the ventricles. The aortic valve did not appear scarred, but was eroded, and presented small, soft, pin-point, grayish-red vegetations which were becoming confluent. Some areas showed marked ulceration, with destruction of valve substance. Similar vegetations were found on the mitral valve, but were less numerous and were limited to smaller areas. The ascending aorta appeared normal except for small flecks of atheroma. In the sinuses of Valsalva there were a few white, thickened areas, with slight longitudinal wrinkling. Just above the right coronary orifice there was a small sacculation, about 5 mm. in diameter, which had a smooth, white lining.

Microscopically, the aortic valve was extensively infiltrated with inflammatory cells (many lymphocytes, some macrophages, and nests of polymorphonuclear leucocytes) which were forming abscesses. Some of the vegetations were firmly attached to the valve by organized tissue while the reaction on the surface was very acute. Most of the valve tissue was very vascular, but there were a few areas of avascular, hyalinizing scar tissue. At the base of the valve, in the sinus portions of the aorta and in the pars membranacea, there were typical syphilitic lesions which were very active, with extensive perivascular lymphocytic infiltration and degeneration of the media. An acute reaction, with fibrin deposition, was seen on the intimal surface of the aorta and on the endocardium overlying these areas of active syphilitic inflammation. A section from the aneurysmal dilatation of the aorta, just above the orifice of the right coronary artery, revealed a small gumma at the junction of adventitia and media. It was composed of a necrotic center, surrounded by fibroblasts, lymphocytes, a few macrophages, and several giant cells. Adjacent to the gumma there was a rift in the wall of the aorta, involving all three layers, which was filled with fibroblastic tissue. A marked perivascular lymphocytic infiltration was present throughout the adjacent portions of adventitia. There was direct continuity between the bacterial process on the aortic valve and that on the mitral valve.

DISCUSSION

In all of the reports dealing with the combination of syphilitic aortic valvulitis and bacterial endocarditis, emphasis is placed upon its great rarity. Although some of the reports state the total number of cases of bacterial endocarditis from which those of a combination with syphilitic valvulitis were gleaned, none of the reports gives the incidence of

syphilitic valvulitis in the source material. Rheumatic fever and congenital anomalies have long been recognized as important predisposing factors in the pathogenesis of bacterial endocarditis. Such a role has not been attributed to syphilis. Yet the common predisposing condition produced by both rheumatic endocarditis and congenital valvular anomalies, namely, morphologic defects and irregularities resulting in valvular deformities, also results from syphilitic valvulitis. It may be that the seeming rarity of syphilis and the apparent frequency of rheumatic fever as predisposing factors in bacterial endocarditis are the result of the difference in incidence, in different localities, of these two diseases as causes of heart lesions. White[26] says, "In New England, for example, rheumatic heart disease makes up an imposing percentage of all types put together, and lues as a factor is relatively unimportant, while among the negroes in the South rheumatic heart disease is far less common and cardiovascular syphilis far more frequent." Most of the reports dealing with the combination of syphilis and bacterial endocarditis come from parts of the world where syphilis is not a common cause of heart disease, although accurate statistics are not available in most instances.

In the Cincinnati General Hospital, during the recent three-year period included in this study (1936, 1937, 1938), syphilitic lesions of some type were diagnosed in 376, or about 16 per cent, of a series of 2,314 routine autopsies. This series included patients of all ages and both sexes from all services of the hospital. Since a large number of the 2,314 autopsies were done on children, and since neither syphilitic aortitis nor syphilitic valvulitis was encountered in any patient under 20 years of age, the factor of age was considered in calculating the incidence of these lesions.

The incidence of rheumatic heart disease with valvular involvement, during the year 1936, was 4.5 per cent (37 cases among 813 autopsies). In eleven, or 30 per cent, of these 37 cases there was a superimposed bacterial endocarditis. Similar statistics for 1937 and 1938 are not available at present.

During the three-year period, sixty-eight cases of syphilitic valvulitis were encountered. In five cases, or 7 per cent, there was a superimposed bacterial endocarditis. Although there was no great difference in the incidence of rheumatic and syphilitic valvulitis (4.5 per cent and 3.7 per cent, respectively, within the age groups in which each occurred) the percentage of patients with the former lesion who developed bacterial endocarditis was over four times greater than the percentage of those having syphilitic valvulitis with superimposed bacterial endocarditis (30 per cent and 7 per cent, respectively). Therefore, the fact that rheumatic valvulitis predisposes to bacterial endocarditis probably depends on some factor other than mechanical defects in the scarred valves.

The relative importance of the known predisposing causes in the eighty-four cases of bacterial endocarditis included in this report is indicated in Table VI.

TABLE V

INCIDENCE OF SYPHILITIC AORTITIS AND SYPHILITIC VALVULITIS IN AUTOPSY CASES AT THE CINCINNATI GENERAL HOSPITAL

	SYPHILITIC AORTITIS WITHOUT VALVULITIS	SYPHILITIC AORTITIS WITH VALVULITIS	TOTAL CASES OF SYPH. AORTITIS
Number of patients	281	68	349
Age 20 years, or older Total autopsies	1793	1793	1793
Age 20 years, or older Incidence	15.6%	3.7%	19.4%

TABLE VI

PRE-EXISTING VALVULAR DISEASE IN AUTOPSY CASES OF BACTERIAL ENDOCARDITIS AT THE CINCINNATI GENERAL HOSPITAL

(1) Rheumatic valvular disease	34 cases
(2) Syphilitic valvular disease	5 cases
(3) Congenital valvular disease	0 cases
(4) Combination of (1) and (2)	5 cases
(5) No evidence of previous valvular disease	*40 cases
	84 cases

*In fourteen of these forty cases there was acute pneumococcus endocarditis.

TABLE VII

INCIDENCE OF SYPHILITIC VALVULITIS IN WHITES AND BLACKS IN AUTOPSY CASES AT THE CINCINNATI GENERAL HOSPITAL

	WHITE	BLACK	TOTAL
Cases of syphilitic valvulitis	28	40	68
Autopsies	1167	626	1793
Incidence	1.6%	6.3%	3.7%

Inasmuch as syphilis is thought to be more prevalent among negroes than among whites, race was considered as a possible factor influencing the incidence of syphilitic valvulitis (Table VII).

Since the incidence of syphilitic valvulitis is about four times greater in blacks than in whites, the incidence of bacterial endocarditis superimposed upon syphilitic valvulitis will probably be greater in hospitals serving large numbers of negroes.

SUMMARY

In the Cincinnati General Hospital, the incidence of syphilitic valvulitis with superimposed bacterial endocarditis has been much greater than that reported in the literature. This high percentage is believed to be a result of the fact that the incidence of syphilitic valvulitis in this hospital is higher than in hospitals serving a smaller percentage of negroes. The incidence of syphilitic valvulitis at autopsy was found to be four times greater in blacks than in whites.

Although rheumatic valvular disease was found to be a more effective predisposing cause of bacterial endocarditis than syphilitic valvular disease, the latter is an important factor, and should be considered clinically in localities with a large negro population and a high incidence of syphilitic valvulitis.

Five autopsy cases of syphilitic valvulitis with superimposed bacterial endocarditis, with no gross or microscopic evidence of rheumatic or congenital heart disease, are presented, and the literature on the subject is reviewed.

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Department of Clinical Reports

PERSISTENT OSTIUM ATRIOVENTRICULARE COMMUNE IN A HEART WHICH FUNCTIONED AS A BILOCULATE ORGAN

Report of a Case, Including Autopsy, in an Eighteen-Year-Old Girl

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THE following case is reported not only because of the unusual lesions disclosed at necropsy, but also because the patient enjoyed a comfortable existence for eighteen years.

Abbott's[1] analysis of 1000 cases of congenital cardiac anomalies lists nine cases of cor biloculare. The maximum age attained was 16 years, the minimum age, 78 hours, and the mean age, 3¼ years. In the same series there were ten cases of persistent ostium atrioventriculare commune in hearts which functioned as biloculate organs (incomplete double heart). The maximum length of life was 4¾ years, the minimum, 2 months, and the mean, 1½ years. We were unable to find any case in the literature in which the length of life approached that of our patient.

REPORT OF CASE

This girl was first encountered Jan. 20, 1927, during a health survey of school children. She was seven years old, undersized and undernourished, and showed the most extreme degree of cyanosis. Her color distinguished her from all the other pupils. A thorough history and examination revealed interesting abnormalities.

She was born at term, and was a "blue baby." She breathed promptly, and was breast-fed for six months. At the age of three years, without provocation, she suffered her first attack of syncope, a phenomenon which recurred at infrequent intervals throughout her life. She was at all times a delicate child, tiring easily, developing and maturing slowly. Running or romping quickly produced dyspnea so pronounced that her contacts with other children were limited. Her disposition was petulant and fretful.

At the age of 6 she had an uneventful attack of whooping cough. At seven, she had varicella complicated by otitis media, from both of which she recovered fully.

The family history was unimportant.

Physical Examination.—The patient was undersized for her seven years, but weighed fifty pounds. She was blue beyond description. The tongue, lips, and buccal surfaces were bluish black. The cheeks were a dark mahogany red. The fingers and toes were extremely clubbed and cold, and the pads at the tips were of much softer texture than the skin over the hands and feet (Fig. 1). The chest, although not well developed, was symmetrical. The expansion of the thoracic cage was bilaterally free and equal. The lungs were normal to physical examination. There were no abnormal pulsations either in the neck vessels or over the chest, nor was a thrill detectable. The apex of the heart was easily located in the left fifth

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intercostal space at the nipple line. The area of cardiac dullness was normal. The heart sounds were clear and sharp. Over the entire precordium, the vessels of the neck, the left axilla, and the lower left scapular area, a soft, blowing, prolonged, systolic murmur was heard; it varied very little in intensity, but was most pronounced at the pulmonic area. The pulmonic second sound was slightly accentuated. The blood pressure was 90/75 in both arms. The cardiac rate varied between 110 and 130, becoming extremely fast on moderate exertion. Examination of the abdomen and nervous system revealed nothing of importance.

Laboratory Examination.—The erythrocytes numbered 8,850,000, the leucocytes, 13,000; of the latter, 69 per cent were polymorphonuclears, 24 per cent lymphocytes, and 5 per cent transitionals. The hemoglobin was 120 per cent (Tallqvist). The coagulation time was seven minutes, thirty seconds; the bleeding time, one minute, forty-five seconds. The urine contained a trace of albumin. The teleoroentgenogram showed slight, general cardiac enlargement, but no striking abnormalities of the organ or of the large vessels. The electrocardiograms at this time are shown in Fig. 2.

FIG. 1.

Course.—The patient was observed at regular intervals for two years, and then was lost sight of for three years because of a change of residence. At the age of 16 she was just past puberty, and, although somewhat short (sixty inches), her secondary development seemed normal. She was not unattractive. The cyanosis was as pronounced as ever, and the clubbing of toes and fingers was more extreme than during infancy. The physical signs remained the same except for a systolic thrill over the pulmonic area, and marked accentuation of the pulmonic second sound. There was now some slight bulging of the precordium, although, fluoroscopically, the heart seemed to be only moderately enlarged to the right. The movements seemed exaggerated. The patient's cardiac reserve seemed to have increased, for she was

now able to compete mildly in games with her classmates. She enjoyed dancing, and was socially popular. She menstruated normally. She suffered frequently from colds and tonsillitis, and tonsillectomy was advised. The tonsils were large, spongy, and exuded pus. The tonsillar nodes were palpable and tender. Her teeth were irregular and diminutive. A routine of mild chest exercises designed to increase the chest muscle development was outlined. Tonsillectomy was performed June 8, 1938. The patient's general condition was satisfactory. She had gained weight (to 101 pounds). The polycythemia was about the same, the clotting and bleeding time unchanged. The patient underwent the operation under local anesthesia satisfactorily. She returned to her home in Virginia, and was in good health until November, 1938, when she suffered a gradual paralysis of the right half of her body, from which she failed to recover. Death in coma ensued.

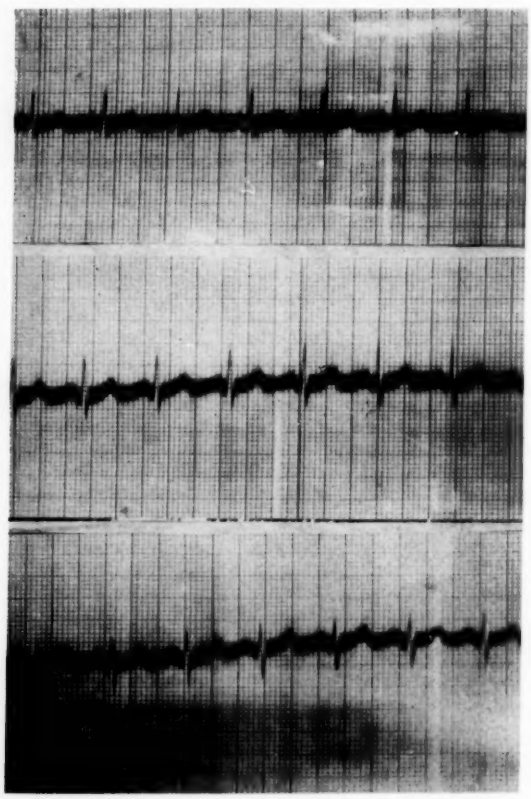

Fig. 2.

Autopsy.—A limited autopsy was permitted, and the heart was sent to us for examination. Unfortunately, the great vessels had been cut off so close to the heart that a study of them was denied us. A description of the heart follows.

The heart was received fixed in formalin. It weighed 223 grams. The greatest anteroposterior diameter was 85 mm., the greatest transverse diameter, 80 mm. Viewed from the anterior aspect, the heart appeared rectangular in shape (Fig. 3). There was more than the usual amount of epicardial fat. The external surface was smooth and glistening except that of the huge right atrium, which presented a roughened, opaque epicardium.

The inferior and superior venae cavae entered the right atrium in the usual manner. The right atrium was markedly dilated. The foramen ovale was functionally and

anatomically closed. Just beneath the foramen ovale there was a large septal defect extending to the atrioventricular valves, allowing free communication between the two atria (Fig. 4). Since there was no interatrial septum in contact with the valves, the mitral and tricuspid leaflets formed a continuous sheet, appearing as a five-

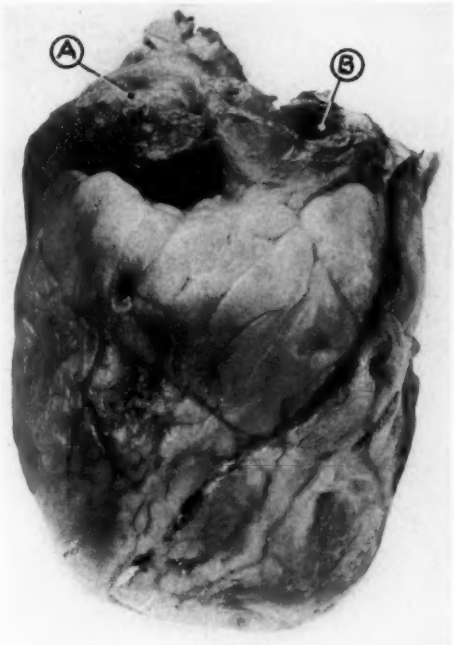

Fig. 3.

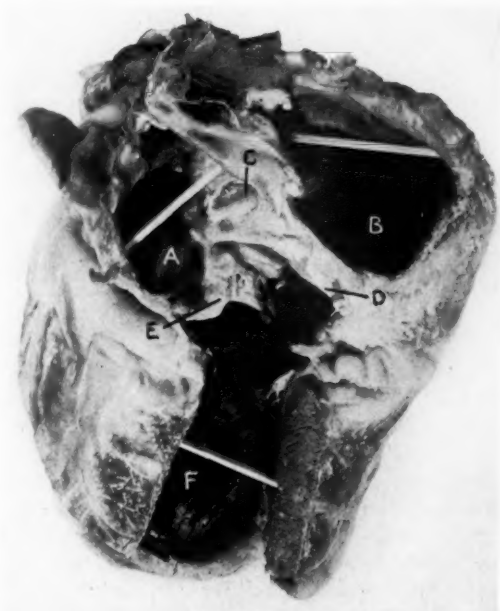

Fig. 4.

leaflet atrioventricular valve, measuring 125 mm. in circumference, and opening into the left ventricle (Fig. 5). The right atrium was several times larger than the left; the latter appeared as a vestigial, horn-shaped projection of the main atrial cavity. The pectinate muscles of the left atrium were small, flabby, and poorly developed, whereas those of the right atrium stood out prominently as well-developed muscle bundles (Fig. 5). The pulmonary veins were thin-walled and small. They entered the left atrium in the usual manner.

The cusps of the pulmonary valve were fused, and the orifice was stenotic, measuring 40 mm. in circumference. The base of the pulmonary artery was very thin and transparent. The right ventricle was almost completely collapsed. There was only a small cone-shaped cavity, 3 cm. deep, beneath the pulmonary valve; the base of the cone was the stenotic valve, and the cavity ended in a completely collapsed ventricle, the muscle bundles of which were interlaced (Fig. 6). The upper, interventricular aspect of this mass of muscle tissue formed the rim of an interventricular septal defect (*A* in Figs. 6 and 7).

The aorta and pulmonary artery had been cut too short to enable us to ascertain whether the ductus arteriosus had been patent. The aortic valve was not remarkable. There was a supernumerary right coronary artery (Fig. 7). The lining of the large coronary arteries was not abnormal. The wall of the left ventricle averaged 10 mm. in thickness, and appeared normal except for the septal defect described above.

Fig. 5.

In addition to the congenital anomalies in this heart, there were small, wart-like nodules along the line of closure of the atrioventricular valves (Fig. 5). The chordae tendineae were thickened and shortened, and there were a few scars on the mitral leaflets.

Microscopic sections from the left ventricle showed no pathologic changes. Sections from the right ventricle revealed moderate atrophy and beginning fibrous replacement. These changes were specially marked in sections taken near the apex. A section of pulmonary artery showed that it was very thin-walled, but otherwise not remarkable. Several sections taken from the atrioventricular valves revealed a sparse lymphocytic reaction in all portions of the valves, most marked in the region

of the line of closure. At this site there were also a marked increase in vascularity and fibroblastic proliferation. Protruding toward the heart's lumen from the line of closure, there was a small thrombus made up of platelets and fibrin, into which

Fig. 6.

Fig. 7.

fibroblasts were growing. No polymorphonuclear leucocytes and no Aschoff cells were seen. One section of valve tissue showed some much older scar tissue, as well as the changes just described.

Final Diagnosis.—Persistent ostium atrioventriculare commune in a heart which functioned as a biloculate organ, presenting a large right atrium and left ventricle; vestigial left atrium and right ventricle; large interatrial and interventricular septal defect; pulmonary valvular stenosis; superimposed subacute verrucous endocarditis of the atrioventricular valves, possibly rheumatic; atrophy and beginning fibrosis of the right ventricular myocardium.

DISCUSSION

There were several interesting features in this case. In the first place, after viewing the cardiac abnormalities, it is difficult to understand how the patient could have lived, with only moderately restricted activity, for eighteen years. From the anatomic abnormalities, it is evident that relatively little blood coursed through the pulmonic artery, and, likewise, that the return from the lesser circulation was small. The lack of circulatory reserve must have been enormous, for the very large atrial and ventricular septal defects insured immediate mixing of the small amount of oxygenated blood with the relatively much larger quantity of venous blood. Yet the patient led a relatively active life.

The physical signs, in the light of the pathologic changes, are quite understandable. The main component of the systolic murmur which was heard over the entire precordia, and was loudest over the pulmonary artery, was no doubt caused by the pulmonic stenosis. The systolic thrill can also be explained in this way. The remaining ridges of the septa no doubt added to the intensity of this murmur. The accentuation of the pulmonic second sound was in all probability caused by the proximity of the pulmonic valve to the chest, and not, in view of the anatomic changes, by pulmonary hypertension.

One is impressed by the normal appearance of the electrocardiogram. Despite marked preponderance of left ventricular tissue, there was no axis deviation. Furthermore, there was no evidence of bundle branch block or intraventricular block.

SUMMARY

A case of persistent ostium atrioventriculare commune in a heart which functioned as a biloculate organ is presented, with autopsy observations. The case history extended over eleven of the patient's eighteen years of life.

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GUMMATOUS MYOCARDITIS AND ANEURYSM OF THE LEFT VENTRICLE

With Nodal Tachycardia, and, Subsequently, Bundle Branch Block

Report of Case

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THE etiologic varieties of ventricular aneurysms are usually stated as being: (1) arteriosclerotic (i.e., following coronary occlusion and myocardial infarction), (2) rheumatic (rheumatic necrosis of myocardium), (3) syphilitic (gummatous myocarditis), (4) mycotic (secondary to bacterial endocarditis), and (5) traumatic. Early observers[1, 2] felt that cardiac aneurysms were most frequently caused by syphilis or rheumatism. Their evidence, however, was often unconvincing, and it is very likely that the majority of their cases would fall into the present arteriosclerotic group. In 1914, Sternberg[3] found that in 84.8 per cent of 207 cases of cardiac aneurysm the cause was coronary occlusion. Since that time, numerous observers[4, 5, 6] have expressed similar views as to the frequency of the association of coronary occlusion and ventricular aneurysm. Syphilitic aneurysm of the heart, however, does occur. In 1935, Sohval[7] collected thirteen cases from the literature and added one of his own. To these fourteen cases we would add three others[8, 9, 10] which were reported before 1935, and one[11] reported in 1936. These, including our case, bring the total of proved syphilitic cardiac aneurysms to nineteen. The present case is unique because there was an associated nodal tachycardia, as well as bundle branch block. Ventricular tachycardia (not nodal) associated with syphilis of the interventricular septum has, to our knowledge, been recorded only once.[12] In this instance, the tachycardia persisted until death, and the lesion in the septum was "sclerogummatous."

CASE REPORT

A. S. (U. 39144), a 30-year-old negress, was admitted to the Medical Service of the Baltimore City Hospitals Nov. 19, 1938, complaining of palpitation of three weeks' duration.

Past History.—The patient had had measles, pertussis, and malaria in childhood. There was also a doubtful history of recurrent epistaxis at about this time. In 1929, at the age of 21, she suffered a severe attack of edema of the ankles and "aching" in her legs, associated with a very sore throat. There was no true joint involvement, and the symptoms had disappeared completely at the end of three months. The patient denied having had any venereal infection, as well as any treatment for syphilis.

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Present Illness: In April, 1938, seven months prior to her admission, the patient noted an aching, burning, substernal pain, associated with a slight, but definite, subjective sense of fever. These associated symptoms occurred invariably at night, and were relieved by alkalies. In August, four months after the onset of the initial symptoms, she noticed, in addition, dyspnea on exertion. There was no edema of the ankles. The dyspnea became progressively worse (the other symptoms remained unchanged), and three weeks before admission to the hospital the patient noticed that her "heart was beating much too fast." This continued until the time of admission, and was the main reason why she came to the hospital. There was no information as to the mode of onset of the tachycardia.

Physical Examination.—The temperature was 101° F., the pulse rate 180, and the respiratory rate 18. The blood pressure measured 80/65 in both arms. The positive findings were limited to the heart. There were diffuse, rippling, systolic pulsations in the second, third, and fourth intercostal spaces to the left of the sternum. The point of maximum impulse was diffuse in the fifth intercostal space, 11.5 cm. from the midsternal line on the left. The heart was markedly enlarged to the left and moderately to the right. A diastolic thrill was felt and a corresponding murmur heard over the mitral area. The remaining cardiac sounds were clearly audible. The heart rate was uninfluenced by carotid sinus pressure. The pulse, although extremely rapid and thready, was regular, and the peripheral vessels were not thickened. The lungs were normal. The liver and spleen were not palpable, and there was no peripheral edema.

Laboratory Examination.—The erythrocyte count was 4.2 million, the hemoglobin 78 per cent (Sahli), the total leucocyte count 6800, and the differential leucocyte count normal. Morphologically, the erythrocytes were normal. The urine was normal. The blood Wassermann and Eagle tests were positive; the spinal fluid Wassermann was negative. The nonprotein nitrogen content of the blood was 31 mg. per cent. The sedimentation rate was 20 mm. in one hour (corrected, Wintrobe). Roentgenographic examination on Nov. 20, 1938, showed that the heart was greatly enlarged to the left and slightly to the right. The pulmonary conus was prominent. There were prominent hilar shadows on the right. The lungs were normal. On Nov. 20, 1938, an electrocardiogram revealed nodal tachycardia, a heart rate of 200 (uninfluenced by carotid sinus pressure), no irregularity, left axis deviation, a P-R interval of 0.07 sec., and a QRS interval of 0.08 sec. In a tracing taken at double speed, P waves were seen preceding the QRS complex by a short interval.

Course.—On admission, the patient was given digitalis and quinidine, both of which were discontinued on the second day. Thereafter, the patient's condition remained unchanged until the fifth hospital day, when she began to complain of abdominal pain, and the liver was found to be enlarged. Two days later she developed edema of the ankles and râles at the bases of both lungs, and digitalis therapy was again begun. The following day (eighth hospital day) the pulse rate, which had stayed persistently around 200, suddenly slowed to 50 to 80 beats per minute, with occasional long pauses between beats, during which time the patient became dazed and dyspneic but never lost consciousness. An electrocardiogram taken at this time revealed a rate of 80; a P-R interval of 0.32 sec.; a QRS interval of 0.14 sec.; aberrant P waves; low voltage in Lead I; a high take-off in Lead III; diphasic T waves directed opposite to the main ventricular deflection in Lead I and Lead III, upright in Lead I and inverted in Lead III; and a wide S in Leads I and III. After the slowing of the rate the diastolic murmur and thrill disappeared. The second pulmonic sound became accentuated. Fluoroscopic examination showed that the heart was greatly enlarged in all diameters, but no aneurysm was noted. The blood pressure declined to 60/50,

and a few hours after the onset of the bradycardia the patient died. The clinical diagnosis was coronary occlusion, with nodal tachycardia and subsequent bundle branch block.

Autopsy Findings (Path. 8538).—Anatomic Diagnosis: Multiple gummata in myocardium of left ventricle; localized gummatous myocarditis and syphilitic pericarditis; fibrous pericardial adhesions; slight hydropericardium; extensive scarring in myocardium (left ventricle); healed gumma in left posterior papillary

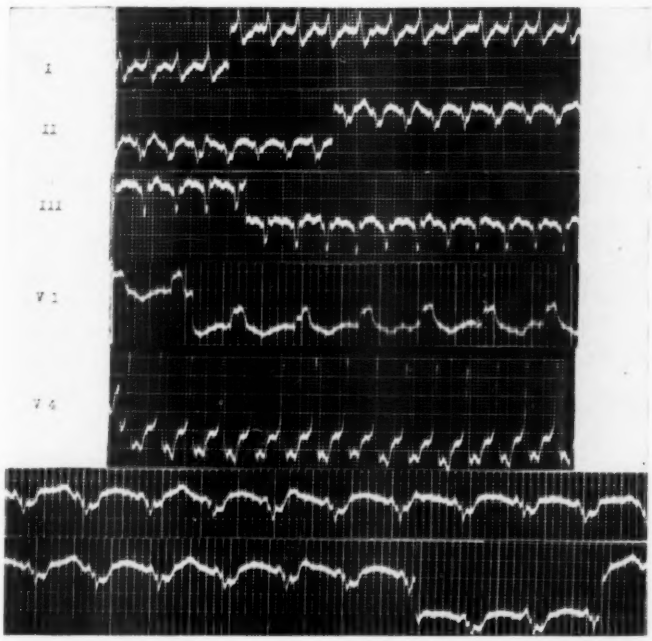

Fig. 1.—Electrocardiogram taken on admission, showing nodal tachycardia.

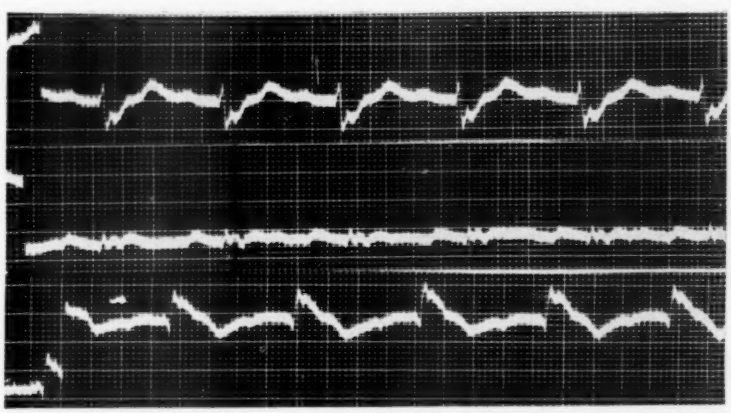

Fig. 2.—Electrocardiogram taken on eighth day after admission, showing bundle branch block. While this tracing was being made, the heart rate varied from 50 to 80, and the patient was having mild Adams-Stokes' attacks. The patient died eight hours later.

muscle; degenerative liquefaction of gumma in base of interventricular septum, with extensive destruction of the region of the conduction system at this level; aneurysm of left ventricular myocardium (posterior); thrombotic material in aneurysm; slight compression of left circumflex coronary artery by gummata in base of left ventricle; numerous areas of fresh and focally calcified myocardial necrosis (infarcts ?); adhesion of tricuspid valve (posterior and medial leaflets) to right ventricular surface of gummatous area in base of interventricular septum; tricuspid valvular insufficiency; marked dilatation and slight hypertrophy of right ventricle; mural thrombi in right auricular appendage; slight hypertrophy of left ventricle; pulmonary edema; hydrothorax (bilaterally); generalized chronic passive congestion; marked central necrosis and atrophy of the liver; fresh necrosis of the hypophysis; diffuse scarring of the pancreas; pelvic peritoneal adhesions; adhesions about capsule of spleen; small, acute ulcer in ileum; localized diphtheritic tracheitis; scars in tonsils; small colloid adenoma of thyroid gland; small hemorrhagic cyst of the ovary; moderate hyperplasia of femur bone marrow; organizing hematoma of the scalp; encapsulated, pulmonary, caseous, tuberculous foci, and tubercles in right apex.

Fig. 3.—Photograph of left ventricle, showing necrotic gumma in interventricular septum immediately below aortic cusps *A*, and aneurysm of the left ventricle posteriorly, *B*. Note scar of gumma in posterior papillary muscle, *C*. There is no syphilitic aortitis.

External Appearance: The body was that of a well-developed, well-nourished negress, approximately 30 years of age. Except for slight edema of the ankles, no abnormalities were noted.

Internal Examination: The large veins at the bases of the heart and neck were distended with blood. Each pleural cavity contained 200 c.c. of clear fluid. The slightly thickened pericardial sac, containing 150 c.c. of clear yellow fluid, was

distended by the moderately enlarged heart. It protruded mainly to the left, so that the base of the left lung was pushed upward and laterally. There was no free fluid in the abdominal cavity. The tubes and ovaries were bound to each other by tough, fibrous adhesions.

Heart (Figs. 3 and 4): The heart weighed 460 Gm. The mitral valve measured 8.5 cm., the aortic valve, 6.5 cm., the tricuspid valve, 11 cm., the pulmonic valve, 7.5 cm., the wall of the left ventricle, 1.4 to 1.8 cm., and the wall of the right ventricle, 0.2 to 0.4 to 0.8 cm. The heart was moderately hypertrophied. There were a patch of old adhesions at the apex and rather numerous tags of old adhesions on the posterior wall of the left ventricle. The right ventricle was tremendously dilated. The right auricle was also dilated, and its dark-red appendage was distended with blood clot and mural thrombi. Beneath the tricuspid valve, at the apex of the interventricular septum, there was a yellowish bulge into the right ventricle, measuring about 2 cm. in diameter. The angle between the medial and posterior leaflets of the tricuspid valve was widened because of the fact that the margin of the posterior leaflet was agglutinated to the surface of the above-mentioned bulging area in the interventricular septum. It is probable

Fig. 4.—Photograph of right ventricle. Arrow points to bulge at the base of the septum. This corresponds to the gummatous region in the interventricular septum seen in Fig. 3. The angle between the medial and posterior tricuspid leaflets is widened at *A*, and the leaflets are agglutinated to the surface of the bulge, thus causing an organic tricuspid insufficiency. At *B*, a portion of the gumma in the posterior myocardium is seen.

that these leaflets were unable to close at the angle. Otherwise, the tricuspid valve was delicate. The mitral, aortic, and pulmonic valves appeared normal. Above and behind the body and posterior leaflet of the mitral valve there was an oval opening, just at the posterior edge of the interventricular septum. The orifice was about 3 cm. in diameter, and had thick, rounded margins. This led into a saeculation, the greatest diameter of which was 5 cm. Its tough and fibrous outer wall was only about 3 mm. thick, and produced quite a bulge on the posterior surface of the left ventricle near the base. The inner surface of the sac had a thin lining of thrombotic material, with a finely corrugated surface. The outer portion of the wall of the sac, as seen through the epicardium, was

mottled a yellow, streaky red, and the appearance was reminiscent of a fresh myocardial infarct. When the heart was held upright, the sac hung flabbily. This aneurysm of the heart wall occupied the same position as that which follows occlusion of the right coronary artery. In this case, however, all of the coronary arteries were delicate and patent, although the left circumflex branch was slightly compressed by gummatous material in the vicinity. Around the margins of the aneurysmal sac there were yellowish-white, opaque, encapsulated masses of rubbery material with some scarring, small hemorrhages, and pigmentation in the nearby myocardium. In a few places this caseous material bulged, and appeared as a healing gummatous lesion. The most extensive involvement of a caseous nature was found at the base of the interventricular septum, anterior to the aneurysmal sac. This area corresponded to the anterior half of the yellow bulge into the right ventricle which has already been mentioned. When this area was incised, a fluid, creamy, light green material was recovered. Benian's and Wright's stains on smears of this material did not reveal spirochetes. After evacuation of the more liquid material, this area in the septum measured 3 × 1.5 cm., and extended through its entire thickness in this area. The remaining necrotic material was soft, and a dark-field examination of it revealed no spirochetes. In the more distal areas of this particular lesion the material was firmer

Fig. 5.—Photomicrograph showing wall of aneurysm in left ventricle, and adjacent myocardium. Dark material lining inner wall of the aneurysm is old thrombus. H and E stain, ×4.

and showed evidence of a greater amount of healing. The uppermost part extended into the lowermost portion of the sinus of Valsalva for approximately 3 mm., but the bases of the aortic cusps were not involved by the process. In the lateral wall of the left ventricle, at a little distance from the large aneurysmal sac, there was a large, depressed scar, measuring 2 cm. in length. The adjacent papillary muscle was shrunken, and the endocardium in this region was a thickened, tough, white layer, 2 mm. deep. Grossly, this lesion was in all probability the result of a large, healed gumma in the myocardium.

Aorta: Except for a few fatty streaks in the intima, the aorta was perfectly smooth. There was nothing to suggest syphilitic aortitis.

Microscopic Lesions.—Heart; wall of aneurysm in left ventricle and adjacent myocardium (see Fig. 5): The wall of the aneurysm was composed of dense lamellae of collagenous connective tissue showing very little inflammatory re-

action, and was reminiscent of the usual appearance of an aneurysm in a vessel. Its inner aspect was completely lined by an even, thin layer of thrombotic material, the outer surface of which was least organized. As the epicardium over the myocardium adjacent to the aneurysm was approached, one was impressed with the numerous, large, focal accumulations of lymphocytes and plasma cells. These were imbedded in the thick but loose epicardial connective tissue, which also contained numerous blood-filled capillaries and small arteries. Practically all of the cellular inflammatory reaction was perivascular. From the epicardium, various-sized, septal, fibrous bands passed into the subjacent myocardium. Some of these likewise contained large focal accumulations of inflammatory cells and small blood vessels. The myocardium in the immediate vicinity of the aneurysm was markedly altered. There were very numerous large and small scars. Many of these were acellular, whereas others contained small clusters of lymphocytes, usually about small vessels. There was also a finer scarring which wove in

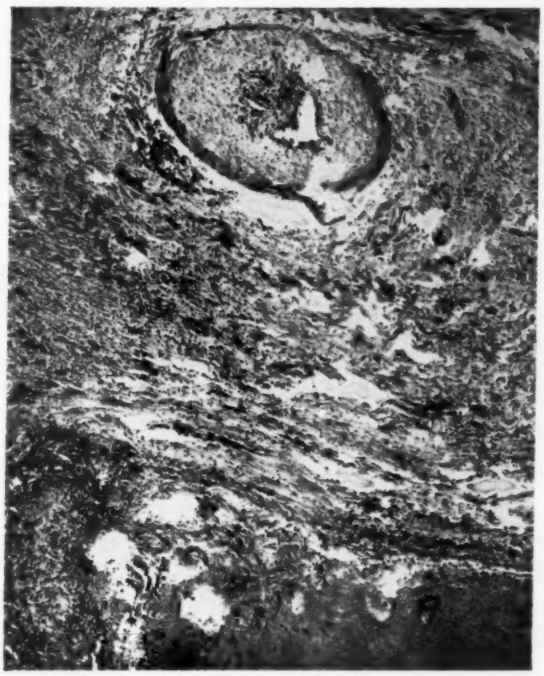

Fig. 6.—Photomicrograph of interventricular septum, showing artery with obliterative changes, surrounded by granulation tissue in which there are numerous plasma cells, as well as occasional giant cells. At *A*, a portion of the more caseous gumma in the septum is seen. H and E stain, ×50.

among most of the myocardial bundles, and occasionally one found small arteries which were the seat of an obliterative endarteritis. In addition, there were changes of a more recent nature. The myocardium contained numerous areas of fresh necrosis. The largest of these were situated directly beneath the myocardium which formed the outer wall of the aneurysm. Here, large bundles of cardiac muscle were fragmented and granular, and had the typical appearance of myocardial infarcts. In one area there was a polymorphonuclear leucocytic reaction which was so extensive that it suggested a purulent inflammatory reaction to pyogenic bacteria. Only a few remnants of muscle fibers were seen here, and these appeared as shadows imbedded in coagulated debris. In this vicinity there were also large clumps of lymphocytes and numerous plasma

cells, together with a small amount of granulation tissue. Bacterial stains failed to reveal any organisms in this region. In another section, a little farther removed, there were numerous areas of focal myocardial necrosis. Some of these had leucocytic margins, whereas others consisted merely of focal polymorphonuclear leucocytic reactions. The oldest necroses appeared as small focal areas of calcification. These were quite numerous, not only in the immediate vicinity of the aneurysm, but also in sections taken at some distance. Numerous sections from the region of the aneurysm were stained by the Levaditi method, but no spirochetes were found. No thrombi were seen in any of the vessels. The endocardium directly continuous with the inner layer of the wall of the aneurysm was irregularly thickened by fibrous connective tissue containing young fibroblasts, moderate numbers of lymphocytes, and a small number of capillaries.

Interventricular Septum (see Fig. 6): There was a thin layer of muscle on the left ventricular aspect which contained numerous areas of focal necrosis and diffuse, perivascular, lymphocytic and plasma cell infiltrations. Beneath this layer, there were rather widespread scarring and a cellular inflammatory reaction. The remaining myocardium of the septum was the seat of a gummatous coagulation necrosis. In the upper part of the septum the necrosis extended almost completely across, and the region of the conduction system was extensively destroyed by the process, but even through this extensive necrosis one could still see the small, irregular specters of myocardium. The margin of the necrotic, gummatous area consisted of a still thin fibrous capsule in which there were great numbers of lymphocytes and plasma cells, as well as a moderate number of polymorphonuclear leucocytes. There were also numerous epithelioid cells, large cells with foamy cytoplasm, and occasional giant cells in the granulation around the capsule of the gumma. In the immediate vicinity, also, a few arteries of various sizes were the seat of an obliterative endarteritis. Serial sections of several blocks prepared after the Levaditi method did not reveal any spirochetes. The acid-fast stain was negative.

Aorta: No changes were found. There was no evidence of syphilis.

DISCUSSION

The case just presented is illustrative of one of the rarer manifestations of cardiac syphilis. Indeed, until 1935, only ninety-seven authentic cases of localized gummatous myocarditis had been reported,[7] and at the present time there are ample indications that in the future this form of visceral involvement will become even rarer, if not extinct.

The differential diagnosis in this case was difficult. Rheumatic myocardial disease, syphilitic myocarditis, and coronary occlusion with aneurysm of the heart were considered. With the disappearance of the murmurs, and with the suggestive electrocardiographic changes, it was thought that coronary occlusion was the most likely possibility. Among the varying entities capable of simulating myocardial infarction clinically, syphilis has occupied an inconspicuous role. Several cases have been reported,[14, 15, 16] however, in which the clinical manifestations were so nearly identical with those of coronary occlusion that the latter diagnosis was erroneously made. Autopsies in these cases revealed no abnormalities of the coronary artery, but, instead, either localized or diffuse gummatous myocarditis. In our case, the clinical evidence of myocardial infarction was exceedingly

unsatisfactory, but, in view of the disparity among the other findings, it was felt that this was possibly an atypical case of coronary occlusion in a relatively young person.

The pathologic changes in gummatous myocarditis have been fully described elsewhere,[7] and it has been pointed out that in these cases the heart may be the only site of syphilitic change. Our autopsy observations revealed localized gummatous changes which were confined exclusively to the heart, with no evidence of syphilis elsewhere. The varying degrees of healing of the individual cardiac lesions accounted for the duration of the patient's history. Unfortunately, the date of the primary syphilitic infection was not known, and there was no history of antisyphilitic treatment. The various fates of cardiac gummata were manifest in this case. The lesion involving the posterior papillary muscle was practically healed, whereas that in the interventricular septum showed not only little healing, but, instead, degenerative liquefaction of most of its central portion. This septal involvement, although extensive, could conceivably have caused only irritation of the conduction system, thus accounting for the tachycardia. Finally, with the spread of the lesion, the region of the upper conduction system was extensively destroyed, and heart block, with the Adams-Stokes syndrome, resulted. In Cossio's case[12] the tachycardia persisted until death, and the septum was the seat of an exudative lesion showing a tendency toward scarring, whereas in our case the process was caseous. Still another end stage of cardiac gummata was represented, namely, aneurysm of the left ventricle. This still showed a small caseous area in one portion of its wall. It is very likely that this cardiac aneurysm was formed by the rupture of a large gumma into the left ventricular chamber. Gummatous involvement of the epicardium rarely accompanies gummatous myocarditis, although focal inflammatory reactions, such as were present in this case, are not infrequently found. Rupture of syphilitic cardiac aneurysms is uncommon; it has been known to occur in only five instances.[7] No spirochetes were demonstrated in any portion of the heart, although numerous Levaditi stains were made. This has been true in practically all such cases. The adhesion of the tricuspid valve leaflets to the gummatous region in the septum probably produced an organic valvular insufficiency, which could have accounted for the dilatation of the right ventricle, as well as the rapid, terminal enlargement of the liver. When gummata involve the valves by contiguity (as in this case), or actually invade the valves, the order of frequency of involvement is pulmonic, aortic, tricuspid, and mitral.[7] The numerous, scattered, fresh and focally calcified areas of necrosis, which appeared as myocardial infarcts in practically all of the sections, were probably caused by small coronary emboli which arose from the thrombus in the wall of the aneurysm, and also, possibly,

by the partial compression of the left circumflex coronary artery by gummata in the base of the heart.

It may be stated, in summarizing, that this case illustrates the fact that syphilis of the interventricular septum can cause nodal tachycardia which may pass terminally into heart block with the Adams-Stokes syndrome. The number of reported cases is too small to justify setting up any diagnostic criteria of gummatous involvement of the myocardium. In fact, it may be completely asymptomatic, and be discovered accidentally post mortem. Gummatous involvement of the heart may be suspected, however, when, with evidence of syphilis, one obtains bizarre combinations of history and cardiac, roentgenographic and electrocardiographic abnormalities. The electrocardiographic changes may be suggestive of those which occur in myocardial infarction.

CONCLUSION

The clinical and post-mortem observations in a case of multiple cardiac gummata and aneurysm of the left ventricular myocardium, with nodal tachycardia, are reported. This is the nineteenth case in which the existence of a syphilitic cardiac aneurysm was proved, and, as far as we knew, represents the first case in which nodal tachycardia was associated with a caseous gumma of the interventricular septum. The cardiac lesions were the only evidence of syphilis in this case.

The authors are indebted to Dr. Frank B. Kindell and Dr. John T. King, Jr., for their advice in preparing this paper.

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CONGENITAL BUNDLE BRANCH BLOCK AS A RESULT, PROBABLY, OF A DEFECT IN THE INTERVENTRICULAR SEPTUM

Report of a Case

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COMPLETE heart block associated with a defect in the interventricular septum is comparatively rare; the subject has been reviewed by Yater and his associates. There are fewer reports of the same defect in association with bundle branch block. This defect belongs in the category of congenital heart disease without cyanosis, and may give no symptoms. In the complete heart block group the slow pulse may attract the interest of the routine examiner and lead to an electrocardiographic examination. In the case here reported, an accidental examination led to the discovery of the defect. Otherwise it would probably have remained undiscovered.

CASE REPORT

Miss B., 26 years old, a laboratory technician, came for a physical examination prior to marriage. She stated that two years earlier she had volunteered as a subject for practice for an electrocardiographic technician, whereupon it was discovered that she had bundle branch block. She was absolutely free of symptoms, and lived an active, energetic life.

She had had measles and whooping cough in childhood. There was no history of rheumatism, chorea, or scarlet fever, or of any other serious disease.

The electrocardiogram was repeated at intervals and showed a constant pattern. The duration of QRS varied in different leads from 0.12 sec. to 0.14 sec. It was of the heterogeneous type.

On physical examination, a moderately loud systolic murmur was heard; it was loudest at the fourth intercostal space to the left of the sternum, and was transmitted over most of the precordium. No thrill was felt. There was no accentuation of the second pulmonic or second aortic heart sound. No splitting of the apical heart sounds could be detected.

The teleoroentgenogram showed some cardiac enlargement to the left. The M.R. diameter was 3.9 cm., and the M.L. diameter, 10 cm., while the width of the chest was 27 cm. The blood pressure was 120/78.

The response of the heart to exercise was normal. There was never any dyspnea or cyanosis, in spite of hard work and vigorous exercise.

DISCUSSION

This case appears to be one of congenital bundle branch block. The constancy of the electrocardiographic pattern, which was uninfluenced by exercise or carotid sinus pressure, makes it most unlikely that the conduction defect was of the functional type. There was no

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history of any disease that could have resulted in endocarditis. The character and mode of transmission of the murmur were characteristic of interventricular septal defect. This anomaly usually causes no symptoms except, at times, a terminal cyanosis. The indefinite type of bundle block is that usually found in association with this defect.

It is thought by some authors that long-continued bundle branch block may cause cardiac hypertrophy. In many cases of congenital heart disease there are multiple lesions, and this must also be considered. Yater and Shapiro[1] reported a case of congenital displacement of the tricuspid valve, with bundle branch block. The patient had many cardiac symptoms, and died at the age of 20 years. The complete diagnosis was made at autopsy.

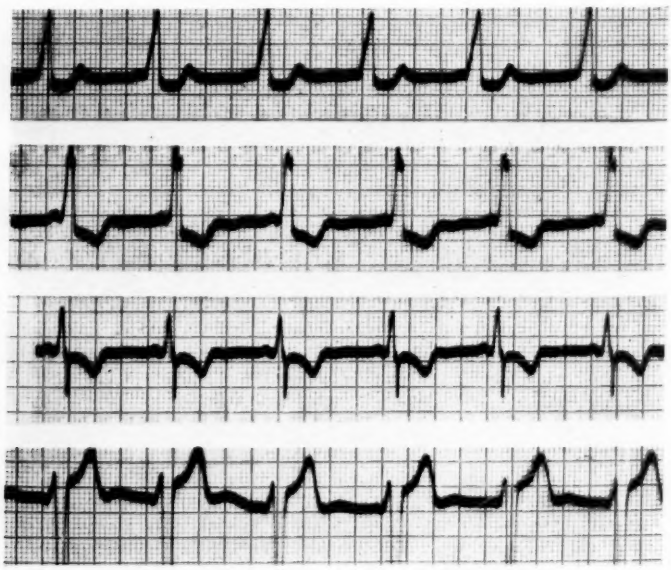

Fig. 1.—Congenital bundle branch block.

It is reasonable to assume that this patient could undertake the responsibilities of marriage and pregnancy without too much danger. She would be assuming a greater risk than a normal woman, and should be prepared to have expert care throughout pregnancy and labor. Jensen,[2] in "The Heart in Pregnancy," states that in cases of uncomplicated congenital septal defect the prognosis is good.

The most serious danger is that subacute bacterial endocarditis might originate at the defect.

SUMMARY

A case of heterogeneous congenital bundle branch block, associated with what is probably an interventricular septal defect, in a woman, 26 years old, is described. This defect at the present time causes no

symptoms, and is compatible with an active, useful existence. It seems reasonable to assume that this patient can withstand the strain of pregnancy without too great a risk.

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Department of Reviews and Abstracts

Selected Abstracts

Scaffidi, Vittorio, Jr.: On the Significance of Venous Pressure Registration by Clinical Methods. I. Relation Between Arterial and Venous Pressure in Normal Conditions of Circulation. Cardiologia 3: 382, 1940.

A description is given of the manometer used for the measurement of the venous pressure, the technique for the measurement is explained, and the arterial and venous pressures simultaneously measured of persons in bed at rest are reported.

The average venous pressure amounts to 91 mm. water. There are no differences with regard to sex. From childhood up to old age the venous pressure declines slowly.

It should be emphasized that there is no distinct relationship between the arterial and the venous pressure. A low pressure on the one hand, lower or higher on the other, may respond and vice versa.

These results are based on the experimental findings of Condorelli, in which the venous circulation is considered as a system with an open outflow. It is confirmed that the visatergo, considered as a preponderant factor in the venous pressure, represents mainly a potential factor which is changed into an actual factor as soon as obstacles arise within the normal circulation.

Under normal circulatory conditions and exclusion of hydrostatic components, the circulatory obstacle is formed by the tone of the venous wall. This tone varies the lumen of the vein by changing a part of the visatergo from a potential into an actual factor.

The venous tone, therefore, determines the value of the venous blood pressure.

AUTHOR.

Turchetti, Aldo: On the Significance of Venous Pressure Registration by Clinical Methods. II. Modification of Pharmacodynamic Action by Substances in Normal Subjects. Cardiologia 4: 85, 1940.

The action of pituitrin, adrenalin, atropine, pilocarpine, histamine, ergotamine, acetylcholine, and nitroglycerin on venous pressure was examined in normal subjects.

Venous pressure was increased by pilocarpine and histamine, and lowered by atropine. Sympathicomimetic drugs increase the pressure, either by a direct action on the muscle coat of the veins (adrenalin) or coincident with the paralyzing action on the sympathetic (ergotamine). Substances increasing directly the tone of the muscle coat of the veins enhance the pressure (pituitrin); those lowering muscle tone reduce venous pressure (nitroglycerin, large doses of acetylcholine).

The fluctuations of the venous pressure are independent of the arterial pressure and of changes of the width of the capillaries.

AUTHOR.

Scaffidi, Vittorio, Jr., and D'Agostino, Lorenzo: On the Significance of Venous Pressure Registration by Clinical Methods. III. The Neurovegetative Regulation of Venous Tone. Cardiologia 4: 107, 1940.

Simultaneous determination of venous pressure and the caliber of superficial peripheral veins of persons in a recumbent position after the administration of neurovegetative effective substances were studied. Venous hypertension caused by pilocarpine, histamine and ergotamine is accompanied with venous constriction. On the other hand, venous hypotension due to atropine is accompanied with dilatation of the veins. Venous hypertension following the injection of adrenalin often shows a simultaneous dilation of the veins; in other cases no change whatever is to be seen in the caliber of the veins. The action of the first four substances proves that chemical excitation of the parasympathicus causes venous constriction and hypertension; wherefore, one is led to the conclusion that the vagus is the cause of the constriction of the veins in opposition to the sympathicus. There is then a regulatory mechanism for venous circulation by means of changes in the tonus of the walls of the veins. The venous circulation, as regards its teleologic effect, is in harmonious combination with the neurovegetative regulation of the arterial tonus.

The hypertension subsequent to the administration of adrenalin, which is not in accord with the conclusions mentioned above, is to be looked upon as a direct muscle effect of the substance of the wall of the vein; the dilatation of the veins observed is to be interpreted as a mobilization of the blood from the depots and, therefore, an increase of the circulating blood.

AUTHORS.

Von A. Huttmann, and Eiser, A.: On the Interpretation of Heart Action Phases on Heart Stroke Frequency. Cardiologia 3: 371, 1940.

The duration of systole and diastole at a heart rate of 45 to 135 per minute was measured in 230 normal subjects. The figure, at increasing frequencies, showed a diminution which follows definite rules.

Aside from Basett's systolic index, a normal diastolic index of 0.56 to 0.62 was observed.

The relationship between duration of diastole and duration of systole was examined. The minute systoles and minute diastoles were obtained by multiplying the duration of systole and that of the diastole by the frequency. Normal figures for the various rates of the heart are given.

AUTHORS.

Wassermann, S.: The Mechanism of Acute Cardiac Pulmonary Edema. Cardiologia 3: 402, 1940.

A case is reported suffering from cardiac pulmonary edema; electrocardiograms were taken during the attack and during a therapeutically successful carotid sinus pressure experiment. The records obtained during the attack and during the pressure on the carotid sinus are not different from the resting electrocardiograms with regard to rate, rhythm, and conductivity. The record taken during the attack shows a diminution of R_1 and R_2 (hypotonia of the cardiac muscle?); this diminution of the R wave disappeared during the carotid sinus pressure experiment.

The attacks are attributed to an insufficiency of the pressoreceptor mechanism; this explains the success of the carotid sinus pressure.

Carotid sinus pressure produced in this and similar cases only a negligible diminution of heart rate (by approximately ten per minute); this is of evidence for the view that carotid sinus pressure in attacks of cardiac pulmonary edema is beneficial through the vascular, and not through the cardiac carotid sinus

reflex. The dyspnea during pulmonary edema is further attributed to presso-receptor insufficiency and not to pulmonary congestion; similarly, the origin of the alveolar edema is not explained as a sign of congestion, but as a consequence of reflex vasopulmonary phenomena (vasospasm, or -paralysis, increases capillary permeability?). This explains the possibility of stopping the attacks (spontaneous improvement; action of morphine or of carotid sinus pressure).

AUTHOR.

Herrington, L. P.: The Heat Regulation of Small Laboratory Animals at Various Environmental Temperatures. Am. J. Physiol. **129**: 123, 1940.

An extensive study of the metabolism of guinea pigs, rats, and mice has identified a region of thermal neutrality at 30 to 31° for the guinea pig, 28 to 29° for the rat, and between 30° and 33° for the mouse. Metabolisms of the order of 590, 680, and 740 calories per square meter per 24 hours, in the same species order, are typical of these temperature ranges.

Above this critical area, the metabolism under hot conditions is very variable, due possibly to the lack of a true physiologic regulation by evaporation. All three species make an effort at adaptation through spreading saliva on their coats, but the success of this process is highly variable.

It has been shown that the metabolic increment with decrease in environmental temperature is species-specific and highly regular. The value of this increment, however, is not in 1:1 correlation with susceptibility to heat loss as judged by surface-weight ratios, and reflects differences in peripheral insulation and probably in response adequacy.

Chemical regulation in these animals is not as completely effective as has been thought. It appears that in spite of large increases in metabolism, the average body temperature falls with decreasing environmental temperature in much the same manner as has been observed in larger animals which do not show chemical regulation in this range. This fall in average body temperature produces failure of regulation when the physiologic limit of storage is reached.

Values are given for surface temperatures in conjunction with known levels of rectal temperature, air temperature, and metabolism. From these values the various conductances, including the environmental heat loss constants, have been computed. Derived values for average body temperature are presented as an illustration of the gradual failure of heat regulation in progressively colder environments.

Theoretical considerations are presented in regard to the practical limit of chemical regulation which suggest that such a limit is not entirely dependent upon the reserve of heat-producing capacity.

AUTHOR.

Seltzer, Carl C.: Body Build and Oxygen Metabolism at Rest and During Exercise. Am. J. Physiol. **129**: 1, 1940.

The results of this investigation with respect to the interrelation of body build and oxygen metabolism may be summarized as follows:

There appears to be a relation of a constitutional nature between morphology of individuals and their consumption of oxygen.

The more "linear" individuals and those with relatively shorter upper and lower extremities, longer torsos, flatter chest outlines, and with narrower hips relative to breadth of shoulders have higher oxygen intakes in the resting state than their "lateral" counterparts. This appears to be the case irrespective of whether the oxygen consumption is related to body weight or surface area.

With respect to moderate exercise smaller oxygen intakes per kilo of body weight are displayed by individuals who are more "lateral" than "linear."

In moderate exercise, greater mechanical efficiency is shown by those individuals whose body build is more "lateral" than "linear."

In exhausting work on the treadmill, greater capacity per kilo of body weight for supplying oxygen to the tissues is shown by those individuals who are more "linear" than "lateral," and who possess shorter upper and lower extremities and longer torsos.

And finally, there seems to be a racial variation as expressed by the craniofacial indices with regard to oxygen metabolism, the exact ramifications of which are not yet clear.

AUTHOR.

Dill, D. B., and Zamcheck, Norman: Respiratory Adjustments to Oxygen-Lack in the Presence of Carbon Dioxide. Am. J. Physiol. **129**: 47, 1940.

The regulation of respiration and the properties of the blood have been studied in two healthy young men exposed to atmospheres deficient in oxygen and containing various concentrations of CO_2. There were significant differences between the two subjects, as is shown by the graphical description of their respiratory responses.

The addition to inspired air of carbon dioxide renders a given low pO_2 more tolerable, not only on account of an increased arterial saturation but because the disturbance of acid-base balance is reduced. However, the gain in oxygen saturation is less than results from an equal increase in pO_2, the pO_2 remaining constant.

The bearing of these and related investigations on current theories of respiratory regulation is discussed.

AUTHORS.

Bazett, H. C., Sunderman, F. W., Doupe, J., and Scott, J. C.: Climatic Effects on the Volume and Composition of Blood in Man. Am. J. Physiol. **129**: 69, 1940.

Exposure of an individual to environmental temperatures maintained at different levels for periods of several days is accompanied by significant changes in blood volume. These changes are found whether blood volume is measured by injection of congo red or T-1824 into the plasma or by the combination of carbon monoxide with hemoglobin. Blood volume is increased in the warmth, decreased in the cold. The changes are associated with changes in the same direction both in the total circulating hemoglobin and in the total plasma protein so that at acclimatization there is little change in their concentrations. The changes in plasma volume develop more rapidly than those in the cells and the initial changes in blood volume are consequently associated with temporary changes in the opposite direction in hemoglobin concentration and hematocrit and sometimes also in the plasma protein concentrations.

AUTHORS.

Burton, A. C., Scott, J. C., McGlone, B., and Bazett, H. C.: Slow Adaptations in the Heat Exchanges of Man to Changed Climatic Conditions. Am. J. Physiol. **129**: 84, 1940.

Data accumulated in four experiments in which the subjects remained for several days in an air-conditioned room kept at either relatively high or relatively low temperatures have been studied to determine the changes in heat exchange and its partition in various channels during slow adaptation to the conditions.

Deep body temperature was maintained at normal levels. A slight shift with new conditions tended to be compensated as acclimatization proceeded.

Average caloric intake was significantly greater in cool than in warm conditions. Foods of higher caloric value per gram, which had a lower equivalent respiratory quotient, were chosen in the cooler conditions. Increased appetite plays a part in acclimatization to cold.

In acclimatization to heat, an increase in the total evaporative loss in the first one or two days is followed by a gradual reduction in later days. This is accompanied by changes in the loss by radiation and convection of a complementary nature, i.e., an initial fall followed by a progressive rise. The latter is associated with the increasing peripheral circulation described in another paper.

When cool climatic conditions follow a period of heat, the evaporative loss which may be supernormal on the first day falls by the third day to a minimum value which is much below accepted standards. In the basal condition this is shown to be explained on physical grounds by the low value of skin temperature reached. The low values maintained throughout the day, however, are physiologically subnormal. The possibility of this subnormality being dependent on osmotic factors is shown. In later days of cold the evaporative loss rises toward normal values.

Radiation and convection are supernormal at the start of a cold period following heat, but fall with the evaporative loss in the first few days. This fall is associated with the slow decrease of skin temperature and peripheral circulation. In later days radiation and convection losses remain at the lower level or rise slightly.

The total heat exchange is deduced from the foregoing and by reference to basal values measured daily. In the heat there is evidence of a slow fall as acclimatization proceeds. In the initial days of cold there is a marked fall followed, after the second or third day, by a steady rise. Correlation of basal metabolic rates with average temperature of the body tissues suggests the operation of hormonal changes, possibly of the thyroid.

Since the increased caloric intake is not accompanied by an increased but by a decreased heat production in the first few days of cold, there is a marked metabolic unbalance on these days. Simultaneously there is a large diuresis continuing for several days and presumably a loss of body fluid, which is to some extent balanced by the storage of food in the body. Weight changes then are less than the changes of fluid content of the body.

Calculations of complete fluid balance are made, but it is shown that these are as unreliable as the weight changes in the absence of metabolic balance.

It is concluded that the processes of acclimatization involve changes in both total heat exchange and its partition. In the heat radiation and convection losses eventually play a greater role, in the cold they decrease as adaptation proceeds. The maintenance of the new partitions involves less strain on the organism after changes of the fluid volume of the body have taken place.

AUTHORS.

Scott, J. C., Bazett, H. C., and Mackie, G. C.: Climatic Effects on Cardiac Output and the Circulation in Man. Am. J. Physiol. **129**: 102, 1940.

Observations on pulse rates, blood pressures, pulse wave velocities, and cardiac outputs calculated from such values, as well as determined by acetylene, are reported in six subjects exposed to moderately warm or cool rooms continuously for several days. The total observations involved eighty-seven subject-days. The reactions of the individuals are found to be modified by their previous thermal history. Two subjects kept in the same room usually reacted similarly. Greater differences were seen between two experiments than between two subjects in any single experiment.

Cardiac outputs with the subjects lying down are increased at first in the warmth and then subside to normal or high normal basal values. In the cold they are at first reduced to subnormal levels and return to normal levels.

Cardiac outputs with the subject standing show marked differences according to the thermal history of the subjects. After adaptation to cool conditions the cardiac output with the subject standing is much below that observed with the subject lying down. In the early stages of warmth this reduction is exaggerated. In later stages of adaptation to warmth there is, on the other hand, little or no such reduction in cardiac output. A series of forty-two observations of cardiac output in the standing posture made on two subjects within a period of two weeks is subjected to statistical analysis to demonstrate this point.

In any given individual these effects of adaptation to warmth may be absent if the subject is dehydrated. Dehydration may exist even though the subject may be free of symptoms at the time of examination.

The differences between the pulse rates while lying and standing are exaggerated in the early stages of exposure to warmth and are reduced later. If exposure to cold follows warmth, they are at first reduced still further, and then later increased.

The efforts of prolonged but relatively mild changes in environmental temperatures on the blood pressures are an initial rise and later fall in the warmth and an initial fall and later rise in the cold. This sequence leads to pressure levels which considerably exceed those control values which precede it. The possible causes are discussed.

Marked difference may be seen in the same subject examined both in the morning and in the afternoon in his reaction to standing. As judged by increases in pulse rate and change in blood pressure on standing, or by cardiac output while standing, an individual may appear to become daily less fit in the mornings on the same series of days during which he appears to be becoming more fit in the afternoons. Fitness tests are complicated by the changes here reported.

The maximal rate of blood flow attained in the fingers steadily increased in a warm room with acclimatization of the subject and reached values much above those commonly found. Warming of the legs decreased, rather than increased, these flows and the decrease was greater, the less the subject was acclimatized. The decrease was also greater if the subject showed signs of dehydration. These changes are attributed to a blood volume relatively inadequate for the demands of the circulation in the early period of exposure to warmth. On exposure to cold several days were required to attain maximal constriction in the fingers. This is attributed to a large blood volume.

The veins of the forearm examined by infrared photographs showed a slight, though somewhat indefinite, gradual increase in size during acclimatization to warmth. They also showed an incapacity to constrict maximally to a mild stimulus of cold in the first few days of such exposure.

AUTHORS.

Schneider, Edward C., and Crampton, C. B.: A Comparison of Some Respiratory and Circulatory Reactions of Athletes and Non-Athletes. Am. J. Physiol. 129: 165, 1940.

When the minute-volume of breathing is stated in terms of square meters of skin surface or in terms of the ventilation equivalent, the economy of the breathing of the athlete is emphasized.

The athlete and nonathlete, during rest and moderate exertion, consume approximately equal amounts of oxygen per square meter of body surface. They also withdraw equal amounts of oxygen from a liter of blood.

The clearest circulatory gains that result from a period of physical training are a reduction in the frequency of heart beat and an increase in the output of the heart per beat. The minute-volume of circulation, when stated in terms of skin surface, seems to be approximately the same for athletes and nonathletes.

The oxygen pulse, when stated in terms of skin surface, gives a good index of differences in heart stroke as found for the athlete and nonathlete.

AUTHORS.

Groedel, Franz M., and Kisch, Bruno: Non-Periodic Variations in the P-R Interval in Man. Cardiologia 3: 365, 1940.

The cases herein described demonstrate that, aside from occasional missing ventricular beats, a poor A-V conductivity is apparent not only in a definitely prolonged P-R interval but, also, in the form of pronounced non-periodic oscillations of the A-V conduction time, due to major or minor variations in the heart rate.

Since the QRST duration does not change in the same sense as the P-R duration, one may conclude that in these cases the A-V conduction system is more easily exhausted than is intraventricular conductivity.

One case of incomplete sinoauricular block with a varying A-V conduction time is reported.

AUTHORS.

Hotz, Von H. W., and Huber, W.: Electrocardiographic Changes in the Course of Acute Diseases of the Tonsil. Cardiologia 4: 40, 1940.

Electrocardiographic studies were made on 100 patients; their average age was 27; sixty-two suffered from acute lacunary tonsillitis, twenty-three from tonsillitis with abscess formation, nine from acute catarrhal tonsillitis and six from acute tonsillitis with Pfeiffer's glandular fever.

Severe changes were found in thirty-one cases; forty patients had slight changes of their electrocardiograms which could not, with certainty, be attributed to myocardial damage. Twenty-nine patients had normal electrocardiograms.

The changes observed were: changes of the conducting time, increase of the duration of the electrical systole, flattening of the T wave, pictures resembling infarction with negative T wave of coronary type. These changes were short-lived.

The electrocardiographic changes found in cases of tonsillitis are nonspecific and can be found during other inflammatory processes. The changes are due, in the majority of cases, to temporary toxic effects on the heart muscle; however, more serious changes, due to myocarditic alterations, may occur and tonsillitis convalescents should be kept off severe physical exertions.

AUTHORS.

Cossio, P., Arana, R., and Kreutzer, R.: Alterations of the Electrocardiogram in Acute Glomerulonephritis. Rev. argent. de cardiol. 6: 283, 1939.

By taking serial tracings in thirty patients with acute glomerulonephritis significant electrocardiographic alterations have been shown to occur in 60 per cent of them. In two cases the histologic study of the heart was made.

Alterations of the P wave consisted in decrease in amplitude, notches, and greater duration. They are thought to be related to an increase in the work of the left auricle due to left ventricular insufficiency.

Alterations of the QRS complex consisted in the appearance of notches deep S_1 waves, deep Q_3 waves, QRS in M or W in Lead III and electrical axis deviations.

They have generally been definitive, and it is important to know that glomerulonephritis, which is a frequent disease in childhood, may be the cause of electrocardiographic abnormalities which persist during the patient's life.

Alterations of the S-T segment are even more significant; sometimes an elevation of this segment in one or more leads occurred due to a coincident pericarditis; in others a depression occurred due to overdistention of one of the ventricles. The depression was more frequently found in Leads I and II and was attributed to left ventricular insufficiency.

Alterations of the T wave consisted in negativity in one or more leads coexisting with or following the alterations in the S-T interval and with the same meaning as these. A coincidence of negative T_3 and T_4 waves was found and an explanation for this finding is suggested.

AUTHORS.

D'Ardois, German Somolinos: Contribution to the Study of Malignant Tumors of the Heart. Arch. latino am. de cardiol. y hemat. **10:** 1, 1940.

Five cases of cardiac sarcomas are presented, one of them primary and the other four of secondary type. The existing literature on this subject also is reviewed, summarizing eighty cases of primary sarcomas which are exhibited in a synoptic table.

The first case was a man 46 years old, with dyspnea, orthopnea, edema of the legs, cough with bloody sputum, palpitation, and cardiac failure. The cardiac sounds remained normal. The x-ray examination showed enlargement of the heart. At the autopsy, a sarcomatous tumor was found, which filled the right auricle and the pericardium in the upper part of the right ventricle; also the apex over the left ventricle. In the interior of the right auricle whose wall was replaced by the tumor, another mass like a nut was observed which was inserted in the interauricular wall. There was presence of blood in both pleurae and the pericardium with metastases in both lungs and in the liver. Histologically the neoplasm was an undifferentiated sarcoma, rich in cells.

Among the four secondary cases, one of them was a pulmonary sarcoma which invaded the heart by direct extension. Another one, of fusocellular type, originated in the kidneys with metastases in the lungs and the heart. A third one, primary in the mediastinal lymphatic glands, was histologically a fibrosarcoma which produced various metastases in the visceral pericardium, and the last one was a melanotic sarcoma with metastases in the myocardium, particularly in the right auricle.

AUTHOR.

Weinstein, W., Plaut, J., and Katz, L. N.: Limitations of the Use of Digitalis for Ambulatory Patients With Auricular Fibrillation. Am. J. Med. Sc. **199:** 498, 1940.

Digitalis, when used in large therapeutic doses, was found to lessen the ventricular acceleration which occurs following a standardized exercise test in ambulatory patients with auricular fibrillation. It also decreased the pulse deficit at the same time. It was not effective in patients who already had a slow ventricular rate. Protracted rest, as well as large doses, may be required to produce slowing.

The tendency to prevent acceleration during exertion and emotional stress represents one of the modes of clinical benefit derived from digitalization.

AUTHORS.

Gold, Harry, and Cattell, McKeen: Mechanism of Digitalis Action in Abolishing Heart Failure. Arch. Int. Med. 65: 263, 1940.

The results of experiments have been presented, and evidence has been adduced for the following statements regarding heart failure and the mechanism of digitalis action by which failure is abolished:

The heart muscle is not overdistended in clinical heart failure. Dilatation of the heart is not usually an unfavorable phenomenon but an adaptive mechanism by which the failing heart maintains its optimum capacity for work.

The high venous pressure in heart failure is not usually a cause but a result of heart failure. There is no sufficient reason for the belief that venous congestion of the order seen in clinical heart failure embarrasses the heart's contraction.

Rapid heart rate in sinus rhythm and auricular fibrillation is usually not a cause but a result of heart failure.

The effect of digitalis in abolishing heart failure is not mediated through any effect on rate in the average case, through action on the splanchnic circulation (constriction of hepatic veins) or through action on cardiac tone.

Digitalis in therapeutic concentrations exerts no direct action on the so-called tone of mammalian heart muscle.

Digitalis improves the function of the heart in heart failure by direct action on the heart muscle, which without primary change in the diastolic length of the muscle increases the tension which the muscle can develop during systolic contraction.

AUTHORS.

Book Reviews

PHYSIOLOGY IN HEALTH AND DISEASE. 3rd ed. By Carl J. Wiggers, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. 1144 pages, 218 illustrations. Philadelphia, 1939. Cloth, $9.50, Lea and Febiger.

The discussion to follow will be concerned only with those parts of Professor Wiggers' book which deal with the circulation. Such parts occupy nearly three hundred pages, and include a discussion of practically all phases of the circulation, both in normal and abnormal states. The author's happy faculty for conciseness enables him to condense a very broad field into a relatively narrow space.

It should be stated at the outset that the book is good in most respects and excellent in many. One of the best features is the bibliography, which is unusually comprehensive. Aside from the frequent references to specific publications in the text, there is appended at the end of each chapter a list of reviews and monographs dealing with the general topics under discussion. These lists of key references have evidently been prepared with great care, and they alone are worth the cost of the book. Although the author states in the preface that the object of his bibliography is to inform the student of the most recent advances rather than to assign credit to specific investigators, his references are so arranged that the reader usually gains a fairly accurate impression of the role played by different workers in the development of a given field. Thus, the important part played by the fundamental work of Garry and of Mines in the development of the concept of circus movements is clearly stated. However, he fails to emphasize the importance of the basic investigations of Wilson and the Ann Arbor group in the development of precordial leads. Such occasional lapses are, of course, inevitable in a book which contains several thousand well-selected references.

The book contains numerous curves derived from experiments, and, in addition, there are many diagrams designed to illustrate particular aspects of circulatory dynamics. These diagrams serve to clarify subjects which would otherwise be difficult for the reader to comprehend. They supplement admirably the author's clear style of writing.

Most good books on scientific subjects can be classified as belonging to one of two types, either the critical review or the monograph. Professor Wiggers' book has the advantage of both—it not only surveys the literature and presents both sides of disputed questions, but it expresses a definite point of view—that of an investigator who has for many years approached the circulation from the standpoint of a physicist. Much of the material dealing with blood pressure, velocity, and the mathematics of the circulation is drawn from his own experiments. There are several chapters which could scarcely have been written by anyone else. These chapters contain practical, as well as theoretical, matter. Thus, the discussions of the roles played by velocity and viscosity in the production of functional murmurs (page 548), of the sources of errors in mercury manometers (page 548), and other topics are more important for the practicing physician than for the physiologist or the medical student. The chapter on heart sounds should be read by every clinician. (Incidentally, Professor Wiggers accepts, practically in toto, the modern "valvular theory," rather than the older "muscular theory," of the origin of the sounds.)

The weakest part of the section on the circulation is that in which the author discusses clinical conditions. Here he falls into the mistake which physiologists frequently make of attempting to draw conclusions concerning chronic diseases from

acute experiments on animals without stating clearly that the factor of time is a very important one and can lead to significant differences between the two conditions. The section on shock is not particularly good, for. although the author cites the various theories, he does not give clearly the most important evidence in support of each. Although the author has ingested most of the literature on shock, he has not digested it completely.

A similar weakness appears in the section dealing with congestive heart failure. He does not seem to understand clearly what the problem of congestive heart failure is as seen in patients. He has very little to say about primary failure of the left side of the heart, and even doubts that this occurs commonly in the absence of failure of the right side. Actually, left-sided failure is much the most common type of heart failure, as every clinician knows. There is a discussion of pulmonary edema, but, in drawing conclusions about it, the author bases his ideas almost entirely on animal experiments. This leads him to conclude that rise in the pulmonary capillary pressure cannot be a dominant factor. Actually, observations of patients indicate clearly that such is the dominant factor. If one is going to discuss clinical conditions one must not only be familiar with observations on experimental animals, but one also needs to interpret such observations in the light of clinical experience.

In spite of these shortcomings in regard to the physiology of diseases, Professor Wiggers' book will be of interest and of value to any clinician who is willing to take the time to study it. The section on the coronary blood flow is excellent, as is the discussion of the dynamics of valve lesions. There is a clear exposition of the mechanism of the paradoxical pulse. Here, as nowhere else, the reader can get a clear conception of the physics of the circulation.

TINSLEY R. HARRISON.

CARDIOLOGIA—PATOLOGIA E CLINICA APPARATO CIRCOLATORIO: By Aldo Luisada, Bologna, 1938, L. Cappelli. 760 pages, 309 illustrations, 120 lire.

This volume represents an attempt to compromise between a short outline and a large monograph on cardiology. The author wishes to offer to a large number of readers the material usually accessible only to specialists. At the same time he presents his own views, based on personal observation and research.

The book is divided into twenty parts. Part One deals with general etiology of the diseases of the circulatory system, Part Two with the methods of taking a complete history and making a physical examination, Part Three with the technical devices used in examining the circulatory system, including mechanical tracings, electrocardiography, phonocardiography, and roentgenology; this is followed by a brief discussion of the value of these methods. Part Four deals with the diseases of the endocardium, and Part Five with the end results of the endocardial lesions—the valvular defects. Part Six is concerned with congenital anomalies of the heart and large vessels. Part Seven deals with syndromes caused by disturbances in rhythm, including tachycardia, bradycardia, arrythmias, and double rhythms, and Part Eight with syndromes caused by diffuse anatomic lesions and disturbances in the contractility of the myocardium. It covers acute and chronic myocarditis, edema of the heart, aneurysms of the heart, tumors and parasites of the heart, and death of the heart. Part Nine takes up coronary insufficiency, infarction, and angina pectoris, Part Ten, diseases of the pericardium and the mediastinophrenic region, Part Eleven, syndromes caused by alterations in arterial pressure, Part Twelve, diseases of the aorta and pulmonary artery, Part Thirteen, diseases of the medium-sized and small vessels, Part Fourteen, vascular neuroses, and Part Fifteen, diseases of the veins. Part Sixteen deals with the effect on the

heart of endocrine disturbances, metabolic disease, avitaminoses, pregnancy, surgical procedures in patients with heart disease, muscular strain, and thoracic deformities. Part Seventeen deals with "complex and associated cardiopathies," Part Eighteen with cardiorespiratory syndromes, such as cardiac asthma, acute pulmonary edema, and periodic and dissociated respiration. Part Nineteen is a consideration of circulatory failure. Part Twenty takes up treatment. It is followed by an appendix on dietetics and on prescriptions.

Among the interesting contributions of the author are the following:

1. The peripheral syndrome of aortic insufficiency is conceived not only as an effect of the valvular lesion, but also as a result of increased active reaction of the peripheral vessels.

2. The use of an esophageal electrocardiographic lead in mitral stenosis, and in chronic sclerosis of the myocardium.

3. A description of some dissociated disorders of the auricles, including simultaneous flutter of the right auricle and fibrillation of the left.

4. An extensive discussion of the clinical and experimental data which indicate that acute pulmonary edema is of neurogenic origin.

5. The section on hypotension and hyposphygmia is summarized from an extensive monograph by the author.

6. The description of circulatory failure constitutes the last chapter, as it may be the final result of any of the circulatory diseases. Evidence is presented against the theory of partial failure of the myocardium.

Included in the book are numerous interesting and original classifications of congenital heart disease, disturbances in the mechanism of the heartbeat, mediastinopericarditis, and low blood pressure.

The illustrations consist of numerous photographs, drawings, and tracings which elucidate clearly the important points in the text. Most interesting are some roentgenograms showing pneumomediastinum in cases of chronic adhesive pericarditis. A large number of the illustrations are from the author's own collection. The material is well organized, outlined, and presented.

Specialized procedures are clarified by being taken up in appropriate chapters; the discussion of percussion, auscultation, phlebography, and cardiography precedes the chapter on valvular defects. Electrocardiography is described before disturbances in rhythm; roentgenology is discussed before the congenital anomalies and diseases of the aorta.

The bibliography is limited to the authors mentioned in the book and to the classical works in cardiology. The index is complete.

M. F. Vidoli.

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THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*